Vol. 21 FEBRUARY, 1947 No. 2

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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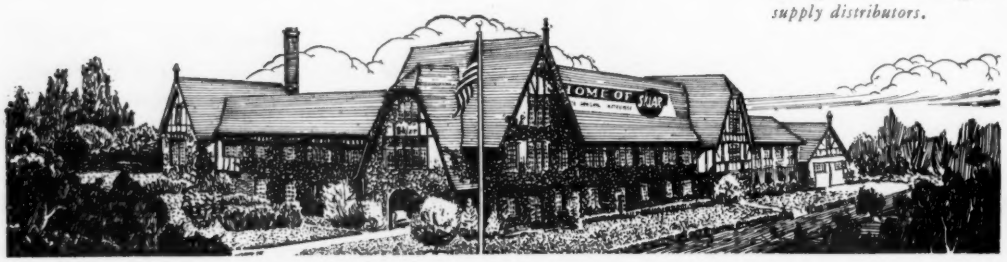

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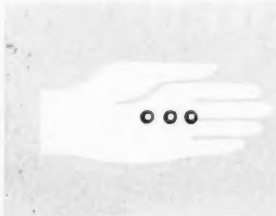

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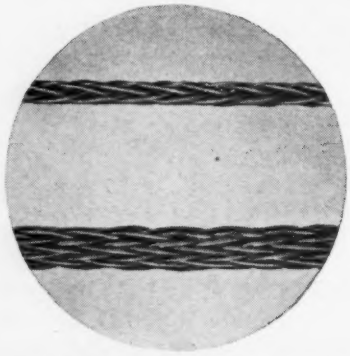

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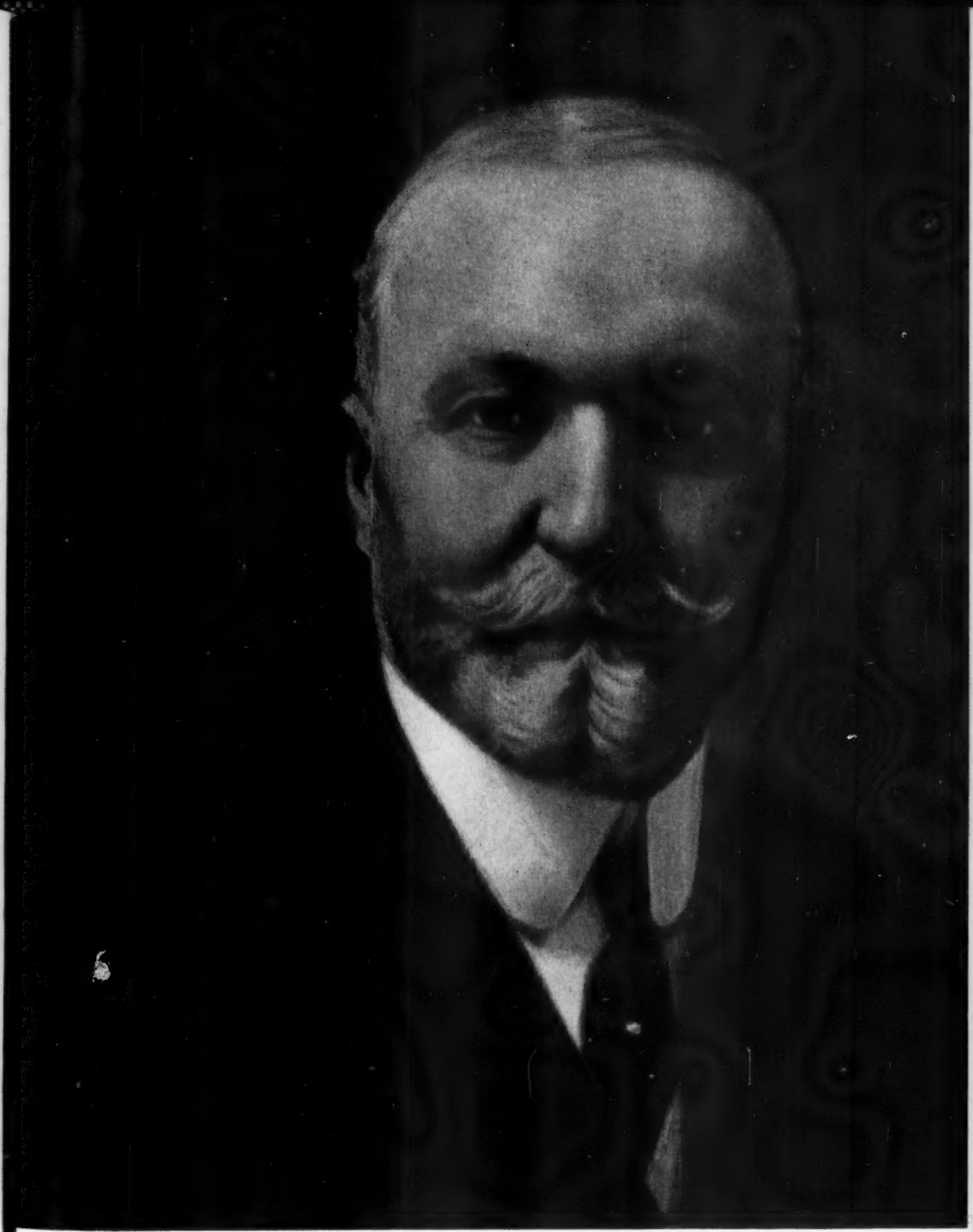

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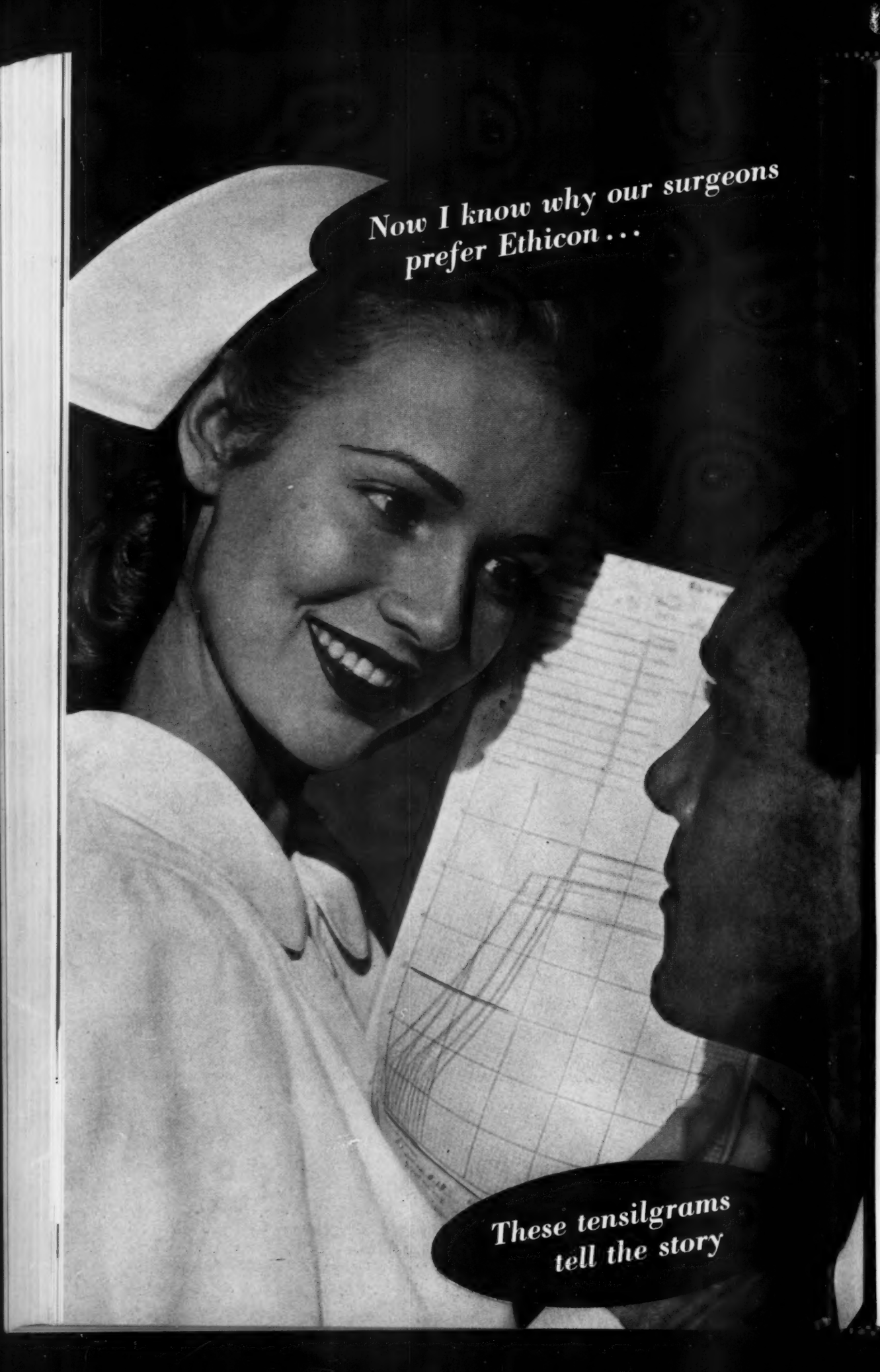
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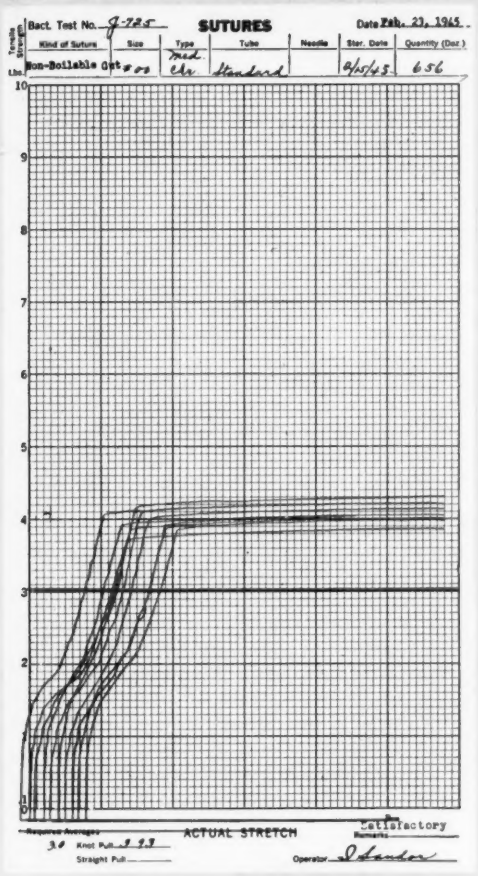

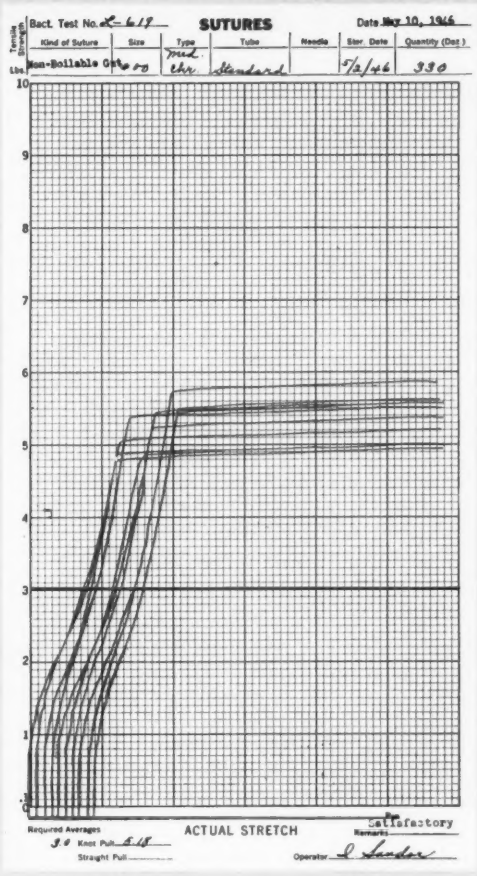

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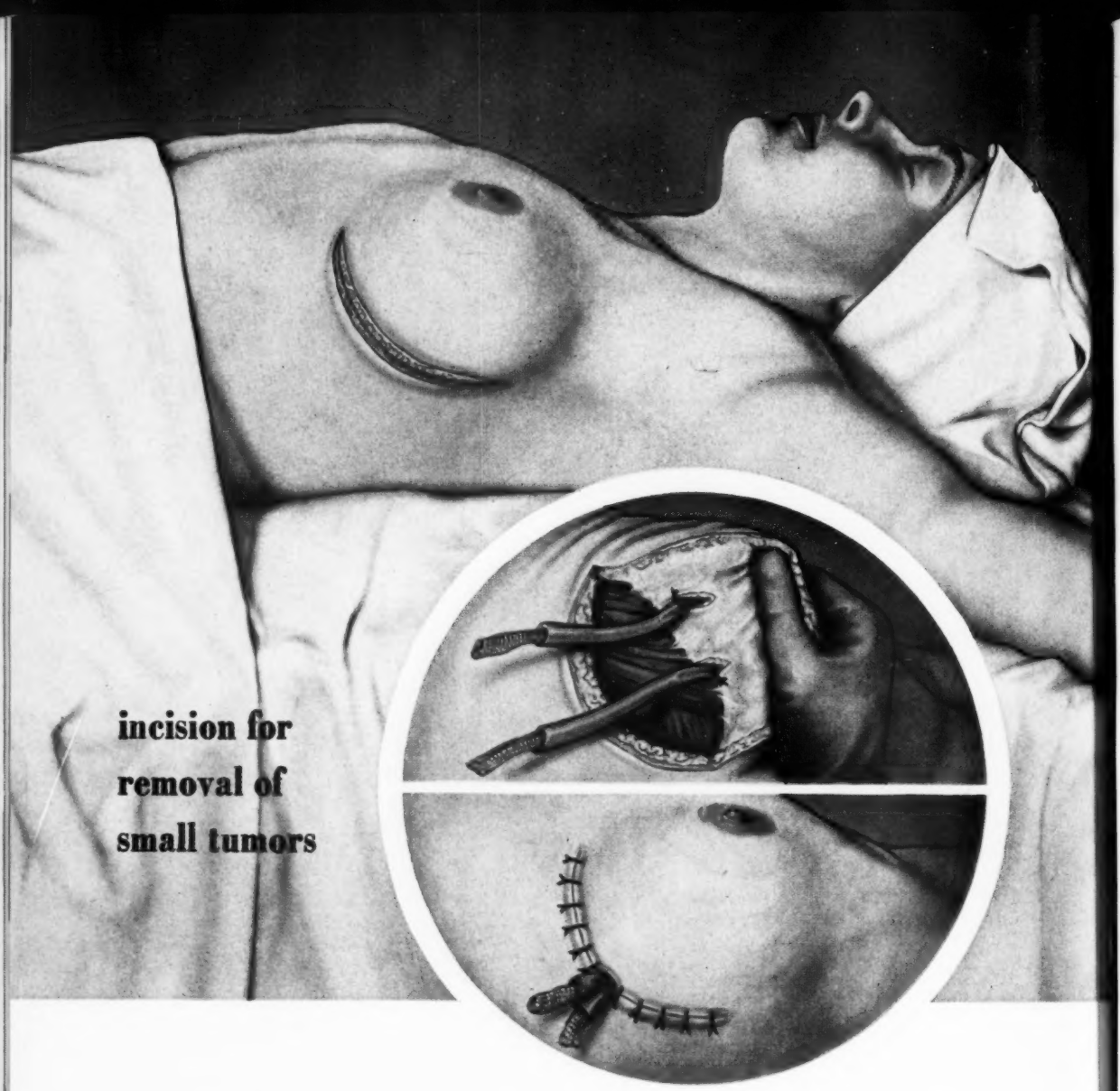

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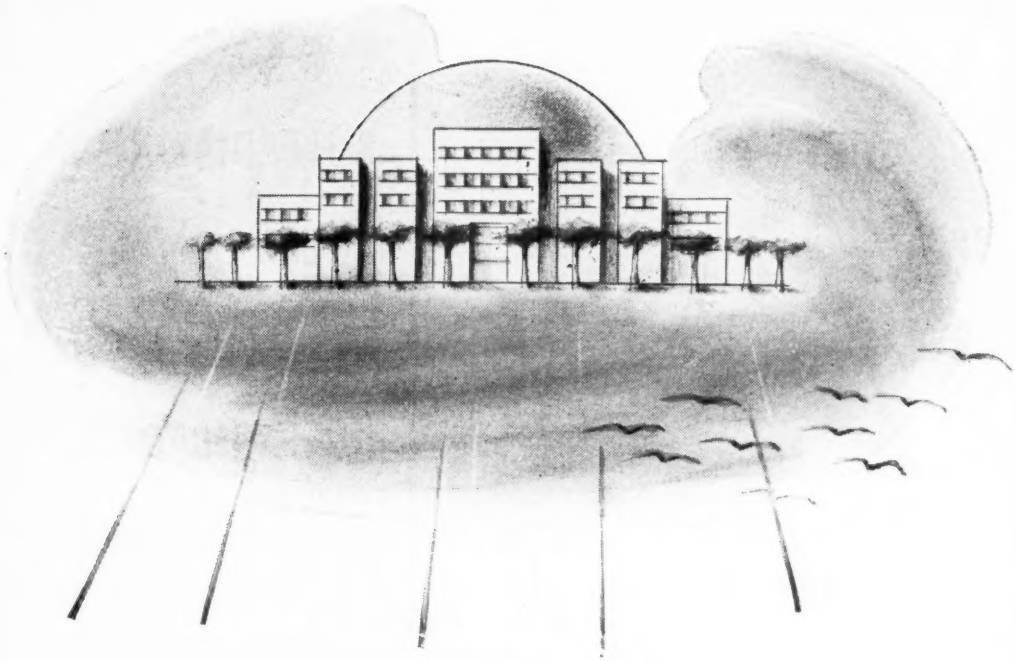

Dream Hospital . . .

The hospital depicted here exists only in the hearts of men and women who are losing the grim battle with cancer. And in the imagination of other men and women who want desperately to provide a haven for these victims in need of hope and care to sustain them in the few months or years still remaining to them.

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SURGERY

VOL. 21 FEBRUARY, 1947 No. 2

Original Communications

EXPERIMENTAL APPENDICAL PERITONITIS

II. THE SIGNIFICANCE OF IMBALANCE OF CIRCULATING FIBRINOLYTIC AND ANTIFIBRINOLYTIC FACTORS IN THE COURSE OF THE DISEASE

JOHN HOWARD KAY, M.D., AND JOHN SALEM LOCKWOOD, M.D.
NEW HAVEN, CONN.
(From the Department of Surgery, Yale University School of Medicine)

THE preceding paper in this series[1] presented certain general observations regarding experimental appendical peritonitis in the dog:

1. It is a disease of local origin which culminates in an acute toxemia characterized by profound disturbances in hemodynamic equilibrium and in impaired function of the liver, lungs, and other vital organs.

2. The systemic character of the morbid response is reflected by shifts in the concentrations of many of the normal constituents of the blood, including water, electrolytes, nonprotein nitrogen, total protein, hemoglobin, and prothrombin.

3. The outcome of the disease, regarding death or survival, appears to be related more to factors inherent in the "condition" of the animal prior to the experiment than to any demonstrable bacteriologic or anatomic variations in the character of the local lesions, as between dying and surviving animals.

4. The animals which survive tend to show no abnormality in prothrombin time immediately prior to the onset of the crisis of the disease, while those which succumb tend to enter the crisis of the disease already handicapped by an abnormal prothrombin time. Fluctuations in the amount of prothrombin, as measured by the Quick method, seem to coordinate in time with fluctuations in the sedimentation rate, the whole blood specific gravity, and the hematocrit.

5. An attempt should be made to explain the correlation which seems to exist between the ability of individual dogs to survive the crisis of pertonitis and the stability, or reversibility, of their prothrombin levels.

The present paper is a report of experiments designed to explore the possible relationship between survival from peritonitis and the antiproteolytic ac-

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tivity of the blood. This avenue of investigation was suggested by relevant inferences drawn from recent work of several investigators, particularly Tagnon, Ferguson, Christensen and MacLeod, and Grob.

Tagnon[2] demonstrated that the fall in blood pressure following the intravenous injection of trypsin is associated with prolongation in prothrombin time and an immediate reduction in the amount of circulating fibrinogen. Both of these reactions could be prevented by the preliminary administration of heparin. Tagnon inferred that the injected proteolytic enzyme converted prothrombin to thrombin, resulting in the intravascular conversion of fibrinogen to fibrin. The absence of formation of macroscopic clots was thought to be due to the fact that the fibrin was deposited as a dispersed film throughout the vascular tree and on the intima of blood vessels. Injection of thrombin caused the same reactions as trypsin, but heparin displayed no neutralizing effect on thrombin, as it did with trypsin.

More recently, Tagnon and his colleagues[3] have pointed out that serum of animals and patients in advanced shock frequently displays increased fibrinolysis and corresponding reductions in fibrinogen and prothrombin levels. Ferguson[4] and others[5, 6] have related the activity of a proteolytic enzyme to the normal blood-clotting mechanism, and have suggested that hemophilia is characterized by a deficiency of this factor.

Christensen and MacLeod[7, 8] have described the properties of a naturally occurring proteolytic enzyme in human serum, which they call plasmin. The mechanism of streptococcal fibrinolysis is the activation of this enzyme by a product of the streptococcus, to which they assign the term streptokinase. In most respects the proteolytic enzyme system of serum is analogous to the proteolytic enzyme systems of the pancreas, trypsin, and chymotrypsin. Serum protease shows important qualitative and quantitative differences with trypsin, but the inhibitors of these two enzymes appear to be similar. Northrop's crystalline pancreatic trypsin inhibitor will inactivate serum proteolytic enzyme, but a larger amount of inhibitor is required in this reaction than is required when crystalline trypsin is employed.

Grob[9, 10] showed that the antiprotease activity of the serum of the rabbit could be substantially increased by the repeated administration to the animal of crude trypsin, either intramuscularly or by mouth. That induced increases in antiprotease activity were of potential significance in disease was supported by the fact that the size of the area of necrosis resulting from subcutaneous injection of trypsin, or of *Staphylococcus aureus,* was inversely proportional to the level of serum antiprotease activity. He confirmed the earlier observations of Wright,[11] and his colleagues, that bacterial growth was often related to the balance between proteolytic and antiproteolytic factors in the media, and showed further that sulfonamide action against *Staph. aureus* was markedly reduced when proteolysis was dominant.[12]

A synthesis of the contributions of these investigators appeared to offer a new approach to an understanding of the basis for the morbid sequences in peritonitis. Tagnon and Ferguson had related abnormalities in the blood-

clotting mechanism, similar to those observed in peritonitis, with activation of a fibrinolytic factor in the blood; Christensen and MacLeod had clarified the relationship between fibrinolysis and serum protease activity and their respective inhibitors; and Grob had shown how an increase in the antitryptic activity of serum could be induced by prolonged administration of trypsin, and that augmentation of antitryptic activity had a definite bearing on the courses of at least two disease entities.

As an initial step in the investigation thus suggested, we have studied by relatively simple methods the fibrinolytic activity of the serum of dogs before and after the production of experimental peritonitis.

METHODS AND MATERIALS

Peritonitis was produced in dogs by ligation of the base of the appendix after freeing this structure from its blood supply. Castor oil was given immediately after operation, and supportive infusions of saline and glucose solution were given every twelve hours. (Full details on technique and management are given in the preceding paper.)

Determination of Fibrinolytic Activity.—We are using the term fibrinolytic activity as an expression of the *net balance* of the factors involved in the lysis of clotted fibrin, namely, the activated plasma proteolytic enzyme (the plasmin of Christensen and MacLeod) and the inhibitor of this enzyme, which has been described as being identical with pancreatic trypsin inhibitor.

Fibrinolytic activity was determined by two distinctly different techniques:

1. By simple incubation of recalcified oxalated dog plasma, at 37° C., determining whether spontaneous lysis of the dog's own fibrin occurred within a period of forty-eight hours. This determination is called serum fibrinolytic activity (SFA).

2. By adding to a standardized preparation of bovine fibrinogen some dog serum which has been treated with chloroform to remove at least a portion of the nonspecific inhibitor of proteolytic enzyme. This procedure (CSFA) permits the measurement of fibrinolytic activity under conditions in which no activity is demonstrable when only unmodified serum is used.[13] In our experiments it is complicated, however, by the fact that the bovine fibrinogen preparation contains a small amount of bovine fibrinolytic enzyme as an impurity.[14] Therefore, fibrinolytic activity as determined in this reacting system is compounded from the combined action of dog and bovine proteolytic factors, on the one hand, opposed by the dog antiproteolytic factor, on the other. In any quantitative expressions of CSFA, the value should, therefore, be considered more as a measure of the amount of proteolytic enzyme inhibitor than as a measure of the amount of the enzyme. An effort is being made to develop an improved technique which will more accurately measure the two factors independently.

Details of the technique employed for measuring SFA and CSFA follow.

Serum fibrinolytic Activity (SFA).—Blood was drawn from the jugular vein into a dry sterile syringe, then transferred to a sterile tube containing 0.5 c.c. of oxalate solution for each 10 c.c. of blood. The oxalate solution comprised

8 Gm. of potassium oxalate and 12 Gm. of ammonium oxalate, per liter. After centrifugation, the plasma was removed into sterile tubes. Plasma, 2 c.c., was placed in a small test tube, and four drops of 2 per cent $CaCl_2$ solution added. Occasional samples failed to clot, a reaction which was not influenced by varying the amount of $CaCl_2$ added (to be discussed later). If a clot formed, the specimen was placed in the water bath at 37° C. and observed for fibrinolysis over a period of forty-eight hours.

Chloroformed Serum Fibrinolytic Activity (CSFA).—Serum was separated from clotted, recalcified plasma, prepared as described previously. One volume of chloroform was added to ten volumes of the serum, and the tube was shaken vigorously by hand for one minute. The tube was then placed in the water bath at 37° C. for one hour, during which a precipitate formed in the lower (chloroform) layer. The specimen was then centrifuged and the supernatant was pipetted off the chloroform layer and placed in the refrigerator at 4° C. for about eighteen hours. The treated serum was then tested for fibrinolytic activity as follows: The serum, 2 c.c., was added to 0.1 c.c. of a solution of bovine fibrinogen* containing 8.6 mg. per cubic centimeter. To this was added 0.5 c.c. of distilled H_2O and, finally, 0.2 c.c. of bovine thrombin (200 units*). The clotted specimen was placed in a water bath and observed for lysis. Lysis occurring in from zero to fifteen minutes was recorded as 4+; from fifteen minutes to one hour, 3+; from one hour to three hours, 2+; and from three hours on, 1+. A reading of 1+ implies little fibrinolytic activity of the dog serum, because the bovine fibrin tended to undergo spontaneous lysis in six to ten hours when only saline solution was added.

Fibrinogen determinations were done by precipitating fibrin by the addition of calcium to plasma diluted with twenty volumes of 0.85 per cent sodium chloride solution. If a clot formed, it was collected on a glass rod, washed, and analyzed for nitrogen by the micro-Kjeldahl procedure. If only a flocculent precipitate formed, it was separated by centrifugation, and analyzed by the same method.

Materials.—The materials used in these experiments were crystalline trypsin,† crude trypsin,‡ bovine fibrinogen and bovine thrombin,§ heparin‖ in Pitkin's menstruum, penicillin,¶ 200,000 units per cubic centimeter in beeswax and peanut oil (Romansky formula[15]).

RESULTS

In Table I are presented the results of determinations of SFA in a series of twenty-seven dogs, among which there were eleven deaths and seventeen survivals. Thirteen of these animals were subjected to several differing methods of treatment (to which detailed reference will be made later) and fourteen were controls. At this point it is desired to indicate only the relationship between

*Supplied by Parke, Davis & Company, Detroit, Mich.

†Obtained from the Plant Research Laboratories, Bloomfield, N. J.

‡Obtained from Armour and Company, Chicago, Ill.

§Obtained from Parke, Davis & Company, Detroit, Mich., through the courtesy of Dr. E. A. Sharp.

‖Supplied by Dr. R. D. Shaner, Roche-Organon, Inc., Roche Park, Nutley, N. J.

¶Obtained from Dr. C. F. Church of the Squibb Institute for Medical Research, E. R. Squibb & Sons, New York, N. Y.

TABLE I. SERUM FIBRINOLYTIC ACTIVITY IN DYING AND SURVIVING ANIMALS DURING COURSE OF DISEASE

DOG NUMBER	HOUR POSTOPERATIVELY							
	PREOPERATIVELY	12	24	36	48	60	72	84
168 NT	−	−	+	No clot	Dead			
170 NT	−	−	+	Dead				
184 NT	+	+	−	+	No clot	Dead		
186 NT	−	+	No clot	Dead				
188 H	−	+	+	+	+	Dead		
190 H	−	−	−	+	+	+	Dead	
193 NT	−	−	−	−	−	−	+	Dead
196 T_4	−	+	−	No clot	Dead			
197 T_4	−	−	−	+	+	No clot	Dead	
207 P	+	+	+	Dead				
209 P	−	+	+	Dead				
172 NT	−	+	+	−	−	−	−	
174 NT	−	+	+	+	−	−	−	
176 NT	+	+	+	+	−	−	−	
178 NT	−	+	+	+	−	−	−	
180 NT	+	−	+	−	−	−	−	
182 NT	−	−	+	−	−	−	−	
192 NT	−	−	−	−	−	−	−	
194 NT	−	−	−	−	−	+	−	
195 T_4	−	−	−	−	+	−	−	
198 T_{12}	−	−	−	−	−	−	−	
199 T_{12}	−	−	−	−	−	−	−	
200 T_{12}	−	−	−	−	−	−	−	
201 P	−	−	−	−	−	−	−	
203 P	−	−	−	−	−	−	−	
205 P	−	−	−	−	−	−	−	
211 P	−	−	−	−	−	−	−	

NT, No treatment.
H, Heparin.
T_4, Trypsin injections for four days.
P, Penicillin.
T_{12}, Trypsin injections for twelve days.
+, Complete lysis within forty-eight hours.
−, No lysis, or incomplete lysis, within forty-eight hours.

measurements of fibrinolytic activity and the course of the disease. The reactions were of two types:

Failure of Clot Formation.—Table I indicates that in five instances the addition of calcium to the oxalated plasma failed to produce a clot. In these cases there developed, instead, a cloudy flocculent precipitate which dissolved in from ten seconds to five minutes. The amount of fibrinogen in these samples was usually greatly reduced. It cannot be stated definitely whether this failure of clot formation was due entirely to fibrinogenolysis or whether some other element in the clotting mechanism was at fault. Significantly, this type of reaction occurred only among the group of animals which died.

Formation of a Clot, Followed by Spontaneous Lysis Within Forty-eight Hours.—The formation of a clot followed by spontaneous lysis within forty-eight hours occurred in at least one of the samples of blood taken from each of the eleven dogs which died. In four instances fibrinolysis occurred in the specimen collected twelve hours before one in which no clot formed upon addition of calcium. One or more positive tests occurred in eight of the sixteen animals which survived. However, in all but two of these the fibrinolytic activity was con-

TABLE II. FIBRINOGEN NITROGEN LEVELS*

DOG NUMBER	HOUR POSTOPERATIVELY						
	PREOPERATIVELY	12	24	36	48	60	72
193	109.0	93.5	90.4	67.4	112.0	112.0	127.1
196	54.6	50.4	74.7	24.2	Died	----	----
197	65.4	63.8	92.6	129.9	129.9	26.2	Died
174	67.8	93.0	94.0	120.3	77.6	126.0	120.3
176	96.4	92.4	101.1	107.1	40.9	99.0	Not done
178	108.0	37.0	111.5	153.0	128.8	150.8	162.8
192	77.0	94.6	123.1	90.2	110.3	111.7	123.0
194	63.8	82.0	43.7	45.4	39.8	118.0	142.4
195	37.2	78.6	119.8	115.3	113.6	88.2	93.8
198	27.7	70.0	76.4	11.0	99.4	69.6	93.5
199	88.7	119.2	115.0	117.5	86.4	119.4	113.0
200	77.2	105.5	113.8	114.8	104.8	94.6	103.2
Average	72.7	81.7	96.3	91.3	94.9	101.4	119.9

*Expressed as nitrogen in milligrams per 100 c.c.; fibrinogen = N×6.25.

fined to the first thirty-six hours of the postoperative period. None of the samples from surviving animals showed fibrinolytic activity at seventy-two hours.

In Table II are depicted the values for fibrinogen nitrogen in blood samples collected at twelve-hour intervals from twelve of the dogs in this group. There was a wide variation between dogs in their preoperative fibrinogen nitrogen levels, and no very consistent trends in subsequent readings can be discerned. The two animals in this group which showed the "no clot" reactions (Dogs 196 and 197) both afforded very low fibrinogen nitrogen readings at that time. Attention is called to the remarkable lability of fibrinogen nitrogen levels in all of the animals. It is possible that this is due not so much to actual fluctuations in fibrinogen concentrations as to variations in the responsiveness of fibrinogen and prothrombin, in diluted oxalated plasma, to the addition of calcium, a potential source of error which is inherent in the method. Of some interest is the fact that average values of fibrinogen nitrogen appeared to be substantially higher after recovery from the disease than before its onset.

Chloroformed Serum Fibrinolytic Activity.—In Table III are presented determinations of fibrinolysis of clots compounded of bovine fibrinogen, bovine thrombin, and dog serum which had been treated previously with chloroform (simultaneous measurements of SFA are shown, for comparison). A reading of 1+ indicates that lysis occurred only after the period of time bordering on that required for lysis of bovine fibrin containing no added serum, and it is safe to infer that fibrinolytic and antifibrinolytic factors were at least in equilibrium with each other. The higher values, 2+, 3+, and 4+ indicate a relative lack of equilibration of these factors, due either to abnormally low antiproteolytic activity or to increased proteolytic activity. The data are arranged according to the stage* of the disease in the individual animal as expressed by his general appearance, rather than according to strict chronology. This arrangement takes into account the considerable variations in the time of onset of the crisis of peritonitis.

*The stages in the course of the experimental diseases are described in the preceding paper.[1]

TABLE III. CHLOROFORMED SERUM FIBRINOLYTIC ACTIVITY AND SERUM FIBRINOLYTIC ACTIVITY, IRRESPECTIVE OF THERAPEUTIC MEASURES

	DOG NUMBER	STAGE I PREOPERATIVE		STAGE II POSTOPERATIVE CRISIS		STAGE III RECOVERY FROM POSTOPERATIVE CRISIS		STAGE IV CRISIS OF PERITONITIS		STAGE V RECOVERY	
		CSFA	SFA	CSFA	SFA	CSFA	SFA	CSFA	SFA	CSFA	SFA
	209 P	3+	–	2+	+	*———		2+	+	Dead, 36 hr.	
	207 P	3+	+	2+	+	*———		3+	+	Dead, 36 hr.	
Died	197 T_4	4+	–	2+	–	*———		4+	+	Dead, 72 hr.	
	196 T_4	3+	–	2+	+	*———		4+	+	Dead, 48 hr.	
	193 NT	2+	–	1+	–	3+	–	3+	+	Dead, 84 hr.	
	190 H	2+	–	4+	–	3+	–	4+	+	Dead, 72 hr.	
	188 H	2+	–	4+	+	*———		4+	+	Dead, 60 hr.	
	192 NT	2+	–	1+	–	2+	–	1+	–	2+	–
	194 NT	1+	–	3+	–	1+	–	3+	–	2+	–
	195 T_4	1+	–	2+	–	3+	–	3+	+	2+	–
	198 T_{12}	1+	–	2+	–	1+	–	1+	–	1+	–
	199 T_{12}	1+	–	1+	–	3+	–	2+	–	2+	–
Lived	200 T_{12}	1+	–	1+	–	1+	–	1+	–	1+	–
	201 P	2+	–	2+	–	1+	–	1+	–	2+	–
	203 P	2+	–	1+	–	2+	–	2+	–	1+	–
	205 P	1+	–	2+	–	2+	–	2+	–	1+	–
	211 P	2+	–	2+	–	2+	–	2+	–	1+	–

Therapy indicated by P. penicillin; T_4, Trypsin for four days; T_{12}, Trypsin for twelve days; H, heparin; NT, no treatment.

CSFA, Chloroformed serum fibrinolytic activity.

SFA, Serum fibrinolytic activity.

*These animals never seemed to recover from the postoperative crisis, but moved directly from Stage II to Stage IV.

It is noted that the levels of CSFA were substantially higher, on the average, in the animals which died than in the animals which survived. All of the six animals with 1+ readings before operation ultimately survived, while the four animals with preoperative readings of 3+ and 4+ succumbed. At the crisis of the disease (Stage IV) six out of seven of the dogs which later died showed values of CSFA of 3+ or 4+, while, in the surviving group, only two out of ten were higher than 2+. Thus, a correlation does appear between the CSFA and the trend toward death or survival. Of greatest significance is the suggestion that this measurement served even before operation to distinguish one group of animals which was able to overcome the disease from another group which succumbed.

Trypsin Administration.—Reference has already been made to Grob's demonstration of the influence of trypsin administration upon the level of the antiproteolytic factor in the blood. If the level of antiproteolytic factor in the blood has a bearing on the resistance of the dog to experimental peritonitis it should be possible to establish this by preoperative administration of trypsin to a group of animals. The results of such experiments are shown in Tables IV and V. The intramuscular injection of 20 mg. of crystalline trypsin for only four days proved to be insufficient to obtain consistent reduction in the level of antiproteolytic activity, as estimated by the CSFA (Table IV). Only one of these three dogs survived, and it happened to be the one with a 2+ reading before operation. Three additional dogs were, therefore, given similar injections of trypsin for twelve days, until the level of CSFA was 1+ in each. These three dogs all survived, and in them the course of the disease was notably modified from that in

TABLE IV. FIBRINOLYTIC ACTIVITY DURING PERITONITIS; TRYPSIN INJECTIONS FOR FOUR DAYS AND TWELVE DAYS PREOPERATIVELY

DOG NO.	DAYS PREOPERATIVE TRYPSIN	PREOPERATIVE		POSTOPERATIVE HOUR							
				12		24 TO 36		48		72	
		CSFA	SFA	CSFA	SFA	CSFA	SFA	CSFA	SFA	CSFA	SFA
195	4	2+	-	2+	-	3+	-	3+	+	2+	-
196	4	3+	-	2+	+	4+	+	Dead		------	
197	4	4+	-	2+	-	3+	+	4+	+	Dead	
198	12	1+	-	2+	-	2+	-	1+	-	1+	-
199	12	1+	-	1+	-	1+	-	1+	-	2+	-
200	12	1+	-	1+	-	1+	-	1+	-	1+	-

three simultaneously studied controls, all of which died. None of the tryspin-injected animals showed signs of collapse at any time; they continued to eat and drink and respond to attention. Unfortunately our supply of crystalline trypsin was then exhausted, no more could be obtained, and it became necessary to resort to a different method of tryspin administration.

Twelve dogs were fed 500 mg. of crude trypsin daily for six days. The trypsin was placed in a capsule and the animal was forced to swallow it under observation. Measurements of SFA and CSFA in three of the dogs afforded indirect confirmation to Grob's observation that the feeding of trypsin would bring about an even more prompt rise in antiproteolytic factor than that produced by injection of the enzyme (Table V). Eleven of the twelve animals so

TABLE V. FIBRINOLYTIC ACTIVITY DURING FEEDING OF TRYPSIN (500 MG. CRUDE TRYPSIN IN GELATIN CAPSULE DAILY)

DOG NUMBER	DAY OF FEEDING					
	1 SFA	2 SFA	3 SFA	4 SFA	5 SFA	DAY OF OPERATION (CSFA)
213	-	-	+	+	-	1+ (Survived)
214	-	+	+	-	-	1+ (Survived)
215	-	+	-	-	-	1+ (Survived)

prepared survived. This was strictly a survival experiment, and detailed measurements of fibrinolytic activity were made in only the three animals depicted in Table V. However, the low mortality rate pointed in the same direction as had the experiment with trypsin injections. Although all but one of the trypsin-fed dogs survived, they did appear acutely ill, and went through a definite disease crisis, in contrast with the three animals which were given trypsin by intramuscular injections and who showed almost no reaction to the disease.

There were, thus, a total of fifteen animals to which trypsin had been given in amounts either demonstrably or presumably sufficient to cause a significant rise in the level of antiproteolytic factor (Table VI). Only one of these fifteen

TABLE VI. INFLUENCE OF PREOPERATIVE TRYPSIN ON MORTALITY OF PERITONITIS IN DOGS

ROUTE	DURATION (DAYS)	NUMBER OF DOGS	SURVIVED	DIED	MORTALITY (%)
Intramuscular	12	3	3	0	0
Oral	6	12	11	1	8.3
Total		15	14	1	6.6
Controls		91	53	38	41.7

animals died from peritonitis. This mortality of 6.6 per cent contrasts favorably with the mortality rate of 41.7 per cent in the ninety-one control animals discussed in the preceding paper.*

Penicillin Treatment.—Reference was made in the preceding paper to the work of Fauley, Duggan, Stormont, and Pfeiffer,[16] who claimed to have demonstrated a significant protective effect with penicillin to the treatment of an experimental disease presumably identical with that employed in our work. They reported a mortality of 92.6 per cent in twenty-seven controls, and no mortality from peritonitis among dogs treated with penicillin, particularly when the drug administration commenced immediately after the operation. However, they excluded from the experimental series twenty-eight animals which died of an internal fecal fistula and four which died of postoperative bronchopneumonia. Recalculation of their data indicates that the over-all mortality of penicillin-treated animals was more nearly 50 per cent, when deaths from all causes were included. In our own experiment the mortality rate among ninety-one control animals was 41.7 per cent, approximately one-half the figure obtained by the Naval investigators. The reason for this difference is not apparent, but it could be related to differences in the types of dogs available, or to the factor of climate, or laboratory temperature.

In an effort to evaluate penicillin treatment under the conditions of our own experiments, peritonitis was produced in fifteen dogs by the standard technique, and injections of penicillin were added to the other measures employed in postoperative care. Each dog was given injections of 50,000 units of penicillin in 0.25 c.c. of the beeswax-peanut oil mixture, commencing immediately after the operation and repeated every twelve hours for five days, so that each dog received 500,000 units of penicillin, a relatively large dose. Random samples of blood were collected for penicillin assay from three of the dogs at various times and the values showed a range of variation from 0.08 units to 1.2 units per cubic centimeter. The number of these determinations was not sufficient to provide any basis for correlation between penicillin level and survival.

Ten of the fifteen animals which were treated with penicillin survived. In Table VII are depicted the results of fibrinolysin studies in six of the animals.

TABLE VII. FIBRINOLYTIC ACTIVITY DURING PERITONITIS; TREATMENT WITH PENICILLIN

DOG NUMBER	PREOPERATIVE		POSTOPERATIVE HOUR							
			12		24		48		72	
	CSFA	SFA	CSFA	SFA	CSFA	SFA	CSFA	SFA	CSFA	SFA
201	2+	-	1+	-	2+	-	1+	-	1+	-
203	2+	-	1+	-	1+	-	2+	-	1+	-
205	1+	-	1+	-	2+	-	1+	-	1+	-
207	3+	+	2+	+	3+	+	Dead		--------	
209	3+	-	2+	+	3+	+	Dead		--------	
211	2+	-	2+	-	2+	-	2+	-	1+	-

*By the time this article was published an additional nine pairs of dogs had been studied; one animal of each pair was prepared with daily injections of a solution of crude trypsin for twelve days and the other served as a control. There were seven survivals and two deaths in the trypsinized group, and four survivals and five deaths in the control group. If these are added to the three pairs in the crystalline trypsin series the mortality rate in the trypsin-injected group becomes 16.6 per cent, and in the paired control group, 66:6 per cent, with twelve animals in each. If all of the trypsinized animals are pooled together the mortality rate of the combined series of twenty-seven animals is 11.1 per cent. The last series of experiments with crude trypsin was performed by Dr. Donald G. C. Clark, and will be reported in detail later.

including four dogs which survived and two animals which died. (These data are also included in Table III.) It is noted that the two penicillin-treated animals which died were those which displayed increased fibrinolytic activity of chloroformed serum before operation.

The results in this limited series of fifteen animals fail to demonstrate any specific protective action by penicillin administered by the technique employed. It is possible that a higher survival rate would have been afforded by giving the penicillin every four hours, as Fauley and his colleagues used it. However, Romansky[15] showed that the beeswax and peanut oil vehicle maintains levels of penicillin for eighteen to twenty-four hours; this, coupled with the fact that we gave at least twice as large a total dosage of the drug as the other workers, makes it unlikely that our results were due to inadequate penicillin treatment.

Heparin Treatment.—Since Tagnon had shown that the reaction to intravenously injected trypsin was modified in heparinized animals, the influence of heparinization on the course of peritonitis was determined in five dogs. The dogs were injected with a single dose of 200 units of heparin in Pitkin's menstruum[17] twelve hours after the operation. The clotting time was maintained above ten minutes for about forty-eight hours. None of the animals survived; the deaths occurred at between 60 and 216 hours following the operation. One factor in the deaths may have been the formation of large hematomas at the sites of the heparin injections.

The SFA in the heparinized dogs appeared to be increased (Table I, Dogs 188 and 190) and these animals, as a group, showed more profound degrees of hemolytic anemia than most of the controls.

On the basis of these discouraging results it was decided that heparin offered no promise as a therapeutic agent in peritonitis, and the work with anticoagulants was abandoned.

DISCUSSION

In the preceding paper it was suggested that survival from this type of experimental peritonitis is largely determined by factors inherent in the make-up of the animal at the time the operation is performed. The normality of the prothrombin time reading during the period of recovery from the immediate effects of the operation afforded a significant basis for prognosis concerning the outcome. In the present paper a correlation has been drawn between survival and the balance of factors concerned in the mechanism of fibrinolysis. Animals which happen to possess a sufficiently high titer of antifibrinolytic factor in the blood, or in which this titer is raised by preliminary administration of trypsin, appear to be best prepared to withstand the deleterious effects of appendical gangrene and peritonitis. The evidence further suggests a correlation between the fibrinolytic-antifibrinolytic equilibrium and the phenomena of erythrocyte sedimentation, intravascular hemolysis, intravascular fibrinolysis, and reduced activity of prothrombin.

These observations offer a new concept of the basis for some of the morbid physiologic processes in peritonitis, and perhaps in other diseases characterized

by a similar shock phase. The evidence is not yet available to indicate what factor in the disease process is ultimately responsible—whether it is the absorption of specific or nonspecific bacterial proteins, the absorption of products of tissue autolysis, or a functional derangement of the liver. Much more work will be needed before this aspect of the subject can be clarified.

Before concluding the discussion, mention should be made of the publications of Knisely and Bloch,[18] of Smith and Smith,[19] and of Mirsky and Freis,[20] which indicate a broader field of application of the phenomena under consideration.

Knisely and Bloch[18] have studied the physical pattern of blood flow in the small vessels and capillaries of the omentum or conjunctiva during the crisis of experimental malaria in monkeys and after severe thermal burns in dogs. In the terminal phases of these diseases the erythrocytes show a tendency to form into conglutinated cords and masses of cells, and the leucocytes tend to adhere to the vascular intima. Marked hemoconcentration and stasis of blood are demonstrable in the capillaries and vessels. Knisely referred to this process as sludge disease. He believed that the initial occurrence leading to sludge formation is the deposition upon erythrocyte surfaces of a sticky film, presumably a fibrinogen derivative, which not only tends to cause adhesion of the cells to one another, but also facilitates the engulfment of the cells by the fixed macrophages. The breaking up of sludge, which may occur rapidly following the institution of effective treatment, is likely to be followed by greatly accelerated destruction of red cells. The observations on peritonitis presented in this paper are compatible with the view that sludge formation occurs in the advanced stages of this disease as well and that the sticky film to which Knisely refers might be a product of the action of a proteolytic enzyme upon fibrinogen or prothrombin. There already exists strong support for the view that the sequence of clotting may be initiated through action of a proteolytic enzyme.[4]

Smith and Smith[19] have demonstrated a fibrinolytic principle in the menstrual discharge, and in the blood of menstruating and eclamptic women, which is highly toxic for small animals. This principle appears to be identical with the "necrosin" which Menkin has prepared from sterile inflammatory exudates. The menstrual toxin can be neutralized by an antifibrinolytic factor which Smith and Smith have found in the globulin fraction of normal plasma protein. This work is cited as additional evidence of the possible significance in other diseases of a disturbance in the equilibration of proteolytic and antiproteolytic factors in animal metabolism.

Mirsky and Freis[20] have suggested, on essentially theoretical grounds, that a proteolytic enzyme may be released or activated when extensive destruction of animal tissues takes place, and that this enzyme "in turn may be responsible not only for changes at the site of injury, but also for the production of catabolic factors whose effect may be reflected in renal, hepatic, and other systemic and functional depressions." An investigation of the influence of antiproteolytic factors upon the phenomenon of increased protein catabolism during acute infection, and after severe trauma, is now in progress in this laboratory.

SUMMARY AND CONCLUSIONS

1. Experimental peritonitis has been produced in 128 dogs, and a search has been made for the factors of greatest significance in determining the outcome of the disease. Preliminary studies in ninety-one control animals have already been reported. This paper concerns an investigation of the significance, in respect to survival, of the balance of fibrinolytic and antifibrinolytic factors in the blood of thirty-seven animals.

2. Evidence of spontaneous lysis of plasma fibrinogen and fibrin occurred with much greater frequency in eleven animals which died (one not measured) than in sixteen animals which survived (nine not measured). Lysis invariably occurred in samples drawn within twelve hours preceding death.

3. Sharp fluctuations in available fibrinogen nitrogen were observed during the course of the disease in all of the animals. The correlation between fibrinogen nitrogen levels and the activity of fibrinolytic factors is not clearly established. Animals which survive show levels of fibrinogen nitrogen approximately 65 per cent greater than preoperative values.

4. The fibrinolytic activity of chloroform-treated serum was significantly higher in dogs which died than it was in dogs which survived.

5. The preoperative administration of trypsin in amounts sufficient to build up the antiproteolytic activity of the serum had a significant influence on survival. Only one of fifteen animals so treated died, which contrasts with a mortality rate of 41.7 per cent in the ninety-one control animals.

6. Neither penicillin nor heparin were of therapeutic value in experiments on small groups of dogs.

7. Some of the literature which bears on this subject is reviewed, and certain of the implications of these results are discussed.

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COEXISTENT DUODENAL ULCER AND GASTRIC MALIGNANCY*

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MEDICAL literature concerning the pathology of the stomach and duodenum is voluminous. It is surprising, however, that references in the literature to the coexistence of malignant lesions of the stomach and duodenal ulcer are very rare. A discussion of this subject was not encountered in any of the textbooks of pathology which were consulted.

REVIEW OF THE LITERATURE

Eusterman and Balfour[1] stated that ". . . in contrast to gastric ulcer which presents the diagnostic and prognostic problem attributable to the ever-present menace of actual or potential carcinoma, the presence of duodenal ulcer is in a certain sense an insurance against gastric carcinoma."

Bockus[2] wrote: "I have found that duodenal ulcer patients with marked gastric hyperchlorhydria and hypersecretion rarely die of gastric carcinoma. I have been in the habit of attempting to dispel a cancer phobia in patients with duodenal ulcer by stating that in my experience patients with this disease are much less likely to develop cancer of the stomach than those who have had no stomach disease whatever."

Smithies and Ochsner[3] had twelve patients in whom gastric carcinoma was coexistent with benign peptic ulcer, in eight of whom the peptic ulcer was in the duodenum.

Wilbur and Rivers[4] in 1932 published a statistical study of thirty-three cases of associated cancer of the stomach and duodenal ulcer which had been encountered at the Mayo Clinic up to that time. They found that the carcinoma of the stomach was the outstanding lesion in all except four of the cases. All of the various types of carcinoma of the stomach were represented in this group. In the group of thirty-three patients, nineteen had active duodenal ulcers, six had perforating or subacute duodenal ulcers, and seven had healed duodenal ulcers. In ten cases the duodenal ulcer was an incidental lesion; that is, it was not suspected before operation or post-mortem examination. There were three cases in which achlorhydria was present and in all three the carcinoma was inoperable. In nine cases the free acid content of the gastric juice was fifty or more. Four patients had undergone gastroenterostomy previously, and one had undergone excision of the duodenal ulcer and pyloroplasty. These authors were able to divide their cases into three groups: those in which the history was definitely that of ulcer; those in which the history was fairly definitely that of

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ulcer; and those in which there were no characteristics suggesting the presence of peptic ulcer.

In 1938 Portis and Jaffé[5] published a report of 9,171 consecutive necropsies performed at the Cook County Hospital in Chicago. In this large group of patients a total of 457 were found to have peptic ulcer; of these, 240 patients had gastric ulcers, 215 had duodenal ulcers, and 2 had jejunal ulcers. Nineteen of these patients had both gastric and duodenal ulcers. None of the patients was said to have a duodenal ulcer associated with a gastric malignant lesion.

Eusterman and Balfour stated that of 15,985 patients undergoing roentgenologic examination of the stomach because of digestive disturbances, 2,047 (12.8 per cent) had deformities of the duodenal cap characteristic of duodenal ulcer. Of these patients, 167 (1 per cent) had roentgenologic evidence of gastric ulcer. In twenty-four cases evidence of both duodenal and gastric ulcers was found. None of these patients was said to have a duodenal ulcer associated with a gastric malignant lesion.

Christiansen[6] reported the gastroscopic findings in seventy cases of roentgenologically verified duodenal ulcers. In forty-nine of these cases he demonstrated definite changes in the gastric mucous membrane. In twenty-one cases the gastroscopic findings were normal. In the forty-nine cases the pathologic changes noted were as follows: gastritis, chronic superficial, thirty-four cases; gastritis, chronic hypertrophic, eight cases; gastritis, atrophic, one case; erosion in normal stomach, five cases; erosion in abnormal stomach, three cases; submucous hemorrhages in normal stomach, one case. Christiansen apparently did not find any cases in which a duodenal ulcer was associated with a gastric malignant lesion.

PRESENT STUDY

Our interest in the study of coexistent duodenal ulcer and gastric malignant lesions was stimulated by seeing at operation a patient whose clinical course strongly suggested the presence of both lesions. Data concerning this patient will be presented with those of others later.

The material for study consisted of records of forty-eight patients having proved coexistent lesions seen at the Mayo Clinic between June, 1911, and January, 1945, inclusive. The criterion for the presence of a duodenal ulcer was the observation of the ulcer at operation or necropsy. The roentgenographic demonstration of a duodenal ulcer was not considered as sufficient evidence for its presence. It is also a fact that when resection of the stomach is performed, a duodenal ulcer is rarely excised; therefore, surgically removed material was of little value in demonstrating or excluding the presence of a duodenal ulcer. The carcinoma of the stomach was verified histologically, except in four cases in which the tissue was not available for study. However, these patients had had lesions which at operation appeared to be carcinoma and they had died within short periods after operation, apparently of carcinoma of the stomach. The microscopic diagnosis of a malignant lesion was based on universally accepted criteria. Epithelial cytoplasia and similar regenerative phenomena about the margins of otherwise benign gastric ulcers were not considered indicative of

carcinoma. There were twelve additional cases in which a presumptive diagnosis of duodenal ulcer and of gastric malignant lesion was made. However, the records in these cases lacked adequate information to satisfy the foregoing criteria. For example, there may have been roentgenologic evidence of both lesions but surgical exploration was not performed.

Incidence.—The forty-eight patients were seen at the Mayo Clinic between June, 1911, and January, 1945, inclusive. During this time approximately 13,000 patients who had carcinoma of the stomach and approximately 45,000 patients who had duodenal ulcer were seen. Approximately 600 patients who had coexistent duodenal ulcer and gastric ulcer were seen during the same interval. Basing an estimate on these figures, it is seen that coexistent duodenal ulcer and gastric malignant lesion occur very rarely. Of the patients having duodenal ulcer, seen at the clinic during this time interval, 1 in 938 (0.1 per cent) had a coexistent gastric malignant lesion. It is difficult to estimate accurately the incidence of duodenal ulcer in the general population. If one accepts the frequently quoted figure of 10 per cent, then the incidence of the coexistent lesions would be about 0.01 per cent in the general population.

The average age of these forty-eight patients was 52.9 years. Three were between 30 and 40 years, sixteen between 40 and 50 years, sixteen between 50 and 60 years, eleven between 60 and 70 years, and two between 70 and 80 years. The youngest was 32 and the oldest was 78 years of age. This age range is about the same as that of carcinoma of the stomach in general.

Of the forty-eight patients, thirty-nine were men and nine were women. This also coincides with the relative occurrence of carcinoma of the stomach in the two sexes.

The duration of symptoms referable to lesions in the stomach and duodenum varied from three days to forty-six years. Among the patients who stated the duration of their symptoms, the average length of time was 11.3 years.

The gastric acidity levels among the forty-eight patients showed a wide range of variations. There did not appear to be any correlation between the degree of gastric acidity and the nature of the peptic lesions. After Ewald test meals, determinations of gastric acidity fell into the following groups: total hydrochloric acid of 50 or more, nineteen patients; total hydrochloric acid between 25 and 50, nineteen patients; total hydrochloric acid less than 25, six patients; free hydrochloric acid absent after Ewald meal, two patients. Determinations of gastric acidity were not made in two cases.

The average hemoglobin level for the group was 12.05 Gm. per 100 c.c. of blood. The lowest hemoglobin level was stated to be 20 per cent of normal and the highest was 17.4 Gm. per 100 c.c. of blood.

Roentgenologic examinations were carried out in forty-six of the forty-eight cases. The diagnosis of coexistent gastric and duodenal lesions was made in twenty-two of the forty-six cases. The filling defect in the stomach was definitely stated to be due to carcinoma in sixteen of the twenty-two cases. The gastric lesions were not visualized in five of the forty-six cases and the duodenal ulcers were missed in eleven cases. The various roentgenologic diagnoses were as follows: carcinoma of the stomach and duodenal ulcer, sixteen cases; gastric

ulcer and duodenal ulcer, six cases; carcinoma of the stomach, seven cases; gastric ulcer, five cases; duodenal ulcer, three cases; pyloric obstruction, one case; lesion at outlet of stomach, two cases; prepyloric lesion, one case; hypertrophic gastritis and duodenal ulcer, two cases; obstruction of the lower part of the esophagus, deformity of cardia, one case; negative, two cases.

Among the forty-eight cases considered in this study, there were four instances of previous operation on the stomach or duodenum. These procedures were as follows: Heineke-Mikulicz pyloroplasty with excision of the duodenal ulcer (carcinoma of stomach thirteen months later); excision of duodenal ulcers on anterior and posterior walls and pyloroplasty (carcinoma of stomach nine years later); posterior gastroenterostomy and appendectomy (carcinoma of stomach ten months later); emergency closure of perforated peptic ulcer (carcinoma of stomach eighteen months later).

Pathologic Findings.—It is difficult to evaluate the nature of the duodenal ulcers in the majority of these cases, because in most instances no tissue was removed from the region of the ulcer for microscopic study. From the surgical descriptions one would assume that the majority of the duodenal ulcers were healed lesions or scars at the time of operation. In only four cases were the duodenal ulcers described as subacute or perforating lesions. The fact that most of the duodenal ulcers were inactive is perhaps significant in that they may have been modified by the presence of the superimposed gastric lesions. In the tissues obtained at post-mortem examination, evidence of duodenal ulcers consisted of scars in two cases, and one chronic duodenal ulcer.

The gastric lesions were predominantly carcinomas. There were one lymphosarcoma and one unclassified high-grade malignant lesion. As previously stated, there were four cases in which the gastric lesions grossly appeared to be carcinomas and were inoperable. No tissue was removed for microscopic study. In each of these four cases the patient died within a short time as a result of what appeared to be extensive carcinoma of the stomach. In the remaining forty-two cases all types of carcinoma of the stomach were represented. In twenty-nine of the forty-two carcinomas the lesion was ulcerating. By Broders' method of grading, the carcinomas were divided as follows: adenocarcinoma, grade 4, ten cases; adenocarcinoma, grade 3, thirteen cases; adenocarcinoma, grade 2, sixteen cases; adenocarcinoma, grade 1, two cases; adenocarcinoma, grade 1, in an adenoma, one case.

The malignant lesions were encountered most frequently along the lesser curvature of the stomach in this group of cases. There did not appear to be any correlation between the nature of the lesion and its location in the stomach. The distribution of the various lesions was as follows: prepyloric region or antrum, eleven cases; lesser curvature, seventeen cases; diffuse involvement, six cases; posterior wall, nine cases; cardiac portion, two cases; anterior wall, one case; greater curvature, one case; microscopic diagnosis of carcinoma associated with diffuse hypertrophic gastritis, one case.

Signs and Symptoms Referable to the Stomach and Duodenum.—In this group of forty-eight cases of coexistent duodenal ulcer and gastric malignant

lesion there were twenty-nine cases in which there were fairly typical symptoms of peptic ulcer preceding the discovery of the malignant lesions by five years or more. In ten cases the symptoms were apparently initially those of carcinoma of the stomach. In the remaining nine cases it was difficult to decide whether the symptoms initially were due to the gastric lesions or to the duodenal ulcers. However, since the majority of the duodenal ulcers were inactive or healed lesions, one would assume that the duodenal ulcers probably preceded the gastric lesions in practically all of the cases.

It was possible to divide the cases in this study into the following four groups according to the nature, progression, and duration of the symptoms: (1) cases in which there was a definite change in the character of symptoms, twenty-four; (2) cases in which there was a change in the degree of severity of the symptoms, fifteen; (3) cases in which the symptoms were progressive, seven; (4) cases in which no changes in the symptoms were noted, two.

It is significant that in this group of patients, the majority of whom suffered from dyspepsia, presumably due to duodenal ulcers, for relatively long periods, only twenty-four noticed a definite change in the character of the symptoms. In this group the changes in the character of the symptoms included one or more of the following: (1) diminution of the relief obtained by taking alkalies or eating food; (2) cessation of periodicity of the abdominal distress or pain, these symptoms becoming more nearly constant than they had been; (3) shift in the location of the pain or the extension of the pain; (4) sensation of rapid filling of the stomach; (5) hemorrhage; (6) abdominal tenderness; (7) palpable abdominal mass.

Survey of Subsequent Course.—It was possible to obtain a follow-up record of forty-seven of the forty-eight patients in this study. Twelve patients were alive more than five years after the diagnosis of coexistent duodenal ulcer and gastric malignant lesion was made, two of the twelve patients being alive twenty and twenty-one years, respectively, after this diagnosis had been established. Of the patients who died, seven died while in the hospital and twenty-two died of gastric malignant lesions at varying intervals.

COMMENT

Although duodenal ulcer and gastric carcinoma are of common occurrence, their coexistence is rare. It is possible that in the presence of carcinoma of the stomach, a duodenal ulcer may be easily overlooked; however, this group of cases demonstrates that the symptoms are usually of long duration and that one would be inclined to search carefully for a benign lesion in the duodenum or stomach. In a number of cases the diagnosis of duodenal ulcer had been established previously and in the majority of the more recent cases both the gastric and the duodenal lesions were demonstrated by the roentgenologist preoperatively.

It has been observed by other workers[1, 2, 4] that a patient who has a duodenal ulcer has relatively good assurance that the likelihood of carcinoma of the stomach developing is rather slight. The clinical data and pathologic specimens in these cases were studied carefully in an effort to determine whether the con-

ditions associated with these duodenal ulcers differed from those of duodenal ulcers in general. It was thought that perhaps hyperchlorhydria or even the bland diet might afford protection against gastric carcinoma for the usual patient having a duodenal ulcer. However, as previously stated, the gastric acidity levels in this group of cases showed wide variation and many of the patients had been under careful medical management. There was no correlation between the gastric acidity and the type or location of the malignant lesion. No conclusion was reached as to why patients who have duodenal ulcers rarely have gastric carcinoma.

It is significant that many of the duodenal ulcers in this series of cases were inactive or healed at the time of operation. Perhaps the development of the gastric lesions produced alterations which tended to heal the duodenal ulcers. Levels of gastric acidity prior to the development of the gastric lesions were not known in most instances. It is possible that in some cases the gastric acidity was decreased as a result of the superimposed gastric lesions.

It is of interest that the survival rate in this group of cases was considerably higher than that usually found in cases of carcinoma of the stomach. It was felt that this was due to the fact that many of the malignant lesions were discovered early. Perhaps patients who have duodenal ulcer are "stomach conscious" and are likely to consult a physician earlier than the average patient who has carcinoma of the stomach.

The symptoms and signs referable to the stomach and duodenum in this group of cases have already been discussed. It is noteworthy that only twenty-four of the forty-eight patients were able to detect a change in the character of their symptoms when the gastric lesions became superimposed on the duodenal ulcers.

SUMMARY

Coexistent duodenal ulcer and gastric malignant lesions are of rare occurrence. In the records of the Mayo Clinic there were only forty-eight proved cases between June, 1911, and January, 1945, inclusive. During this interval, approximately 45,000 patients who had duodenal ulcer and approximately 13,000 patients who had carcinoma of the stomach were seen. Of the patients having duodenal ulcer seen at the Mayo Clinic, 1 in 938 (0.1 per cent) had a coexistent gastric malignant lesion.

The age and sex incidence was about the same as that of carcinoma of the stomach in general.

The symptoms were of long standing in the majority of cases, varying from three days to forty-six years. The average duration of symptoms was 11.3 years.

There did not appear to be any correlation between the levels of gastric acidity and the nature of the peptic lesions. There was wide variation in the levels of gastric acidity encountered.

The roentgenologic diagnosis was accurate in a large percentage of the cases, particularly those in which the examination was made within recent years.

Four of the forty-eight patients in this group had undergone previous surgical treatment of the stomach or duodenum.

It was difficult to evaluate the exact nature of the duodenal ulcers in most of the cases, because in most instances no tissue was removed from the duodenal ulcer for microscopic study. Subacute or perforating duodenal ulcers were described at operation in only four instances. It was assumed that the remaining duodenal ulcers were chronic or healed lesions.

The gastric lesions were predominantly carcinomas. There were one lymphosarcoma and one unclassified high-grade malignant neoplasm. The diagnosis of carcinoma was based on universally accepted histopathologic criteria. Several cases of previously diagnosed carcinoma of the stomach were discarded because it was felt that the histologic changes represented regenerative changes rather than carcinoma.

No explanation could be derived when an effort was made to determine why patients who had duodenal ulcers seldom have malignant lesions of the stomach.

The survival rate in this group of cases was considerably higher than that usually found in cases of carcinoma of the stomach. This was explained by the fact that patients who have duodenal ulcer are "stomach conscious" and are inclined to consult a physician early.

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THE USE OF STREPTOMYCIN IN SURGICAL PATIENTS

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IN THE treatment of infections caused by gram-negative bacteria, streptomycin promises much the same therapeutic effectiveness that penicillin has manifested in the treatment of infections caused by the gram-positive organisms. It remains to be demonstrated whether or not this impression gained from in vitro experiments is confirmed by clinical experience. Although streptomycin is effective in the treatment of certain gram-positive organisms, in general, its effectiveness against these organisms is not as great as that of penicillin. Data, which we wish to summarize, have been obtained by a group of individuals working on several phases of this problem at the University of Pennsylvania.

Streptomycin, first described by Waksman and associates,[6] is obtained from cultures of *Actinomyces griseus*. It is distributed for investigational purposes as a powder varying in color from gray to brown and varying in potency from 200 to 450 units per milligram. A white crystalline material has been prepared which has a potency of 1,000 units per milligram and is now used as a standard of reference but is not available for clinical use. One microgram of this pure material is equivalent to one streptomycin unit. Thus, 1.0 Gm. is equivalent to 1,000,000 units, a moderate daily dose.

Studies of the acute toxicity of streptomycin indicate that it is definitely more toxic than penicillin, but, nevertheless, the margin of safety between the therapeutic and a definitely toxic dose is wide. Acute toxic symptoms, including palpitation, headache, flushing of the skin, arthralgia, and delayed fever, often occur at dosage levels of 4.0 to 5.0 Gm. per day when given in divided doses intramuscularly, and tend to limit the dosage to less than 4.0 Gm. per day. No evidence of toxicity has been noted following oral administration. Patients have been studied for possible acute toxic effects on the liver, kidney, and cellular constituents of the blood following the intravenous injection of 0.6 Gm. of streptomycin.[1] In six patients, liver function was studied by the bromsulfalein retention, hippuric acid conjugation, quantitative van den Bergh, blood cholesterol, cholesterol-cholesterol ester ratio, prothrombin time, cephalin flocculation, colloidal gold, and thymol turbidity tests before and after the administration of streptomycin. Table I shows that no significant changes in the average values of these tests resulted.

Kidney function as evaluated by per cent of average normal urea clearance, blood urea nitrogen, and blood nonprotein nitrogen showed no significant differences after the administration of streptomycin, as shown in Table II. In addition, routine urinalyses before and every three hours for twenty-four hours after

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TABLE I. EFFECT ON LIVER FUNCTION OF THE INTRAVENOUS INJECTION OF 0.6 GM. STREPTOMYCIN: AVERAGES OF RESULTS IN SIX PATIENTS

TESTS OF LIVER FUNCTION	BEFORE STREPTOMYCIN	24 HOURS AFTER STREPTOMYCIN
Bromsulfalein (retention in 30 min.)	3.3	1.7
Hippuric acid conjugation (grams excreted)	1.8	1.4
van den Bergh (milligram of bilirubin)	0.3	0.4
Serum cholesterol	142	151
Cholesterol ester (per cent)	60	63
Prothrombin time (per cent of normal)	77.5	81.7
Cephalin flocculation	Neg.	Neg.*
Colloidal gold	Neg.	Neg.*
Thymol turbidity	Neg.	Neg.*

*Forty-eight hours after streptomycin.

the administration of the streptomycin showed no significant changes. The values of the constituents of the blood as tabulated in Table III show essentially no changes in ten patients.

TABLE II. EFFECT OF 0.6 GM. STREPTOMYCIN ADMINISTERED INTRAVENOUSLY ON RENAL FUNCTION OF SIX PATIENTS

RENAL FUNCTION CRITERIA	AVERAGE BEFORE STREPTOMYCIN	TWENTY-FOUR HOURS AFTER STREPTOMYCIN
Normal urea clearance (per cent of average)	99.1	80.1
Blood urea nitrogen (milligrams per cent)	10.7	9.2
Nonprotein nitrogen (milligrams per cent)	24.3	24.5

Urinalyses every three hours for a period of twenty-four hours after the injection of streptomycin showed no changes.

The only types of chronic toxicity observed clinically have been deafness and vertigo, which have been reported by Hinshaw and Feldman[2] in tuberculous patients who had had large daily doses for several consecutive months. We have noted no evidences of latent toxicity in approximately one hundred patients to whom we have administered the material. In these patients, the largest total dose was 35.0 Gm. over a seven-day period, and the average total dose was approximately 12.5 Gm. over a ten-day period.

TABLE III. EFFECT OF THE INTRAVENOUS INJECTION OF 0.6 GM. STREPTOMYCIN ON THE BLOOD IN TEN PATIENTS

BLOOD COMPONENTS	AVERAGE BEFORE STREPTOMYCIN	AVERAGE 24 HOURS AFTER STREPTOMYCIN
Hemoglobin (Klett photoelectrometer)	85.6%	82.2%
White blood cells	6,840	6,990
Neutrophiles	71.1%	71.0%
Eosinophiles	0.4%	1.2%
Lymphocytes	27.9%	26.4%
Basophiles	0.0%	0.0%
Monocytes	1.6%	2.4%

ABSORPTION, DISTRIBUTION, AND EXCRETION

The absorption, distribution, and excretion of streptomycin in the body depend on the route of administration. When administered orally, approximately 95 per cent was recovered in the feces, and less than 2 per cent was recovered in the urine. Following parenteral administration, an average of 66 per cent of the amount injected was recovered in the urine, and less than 2

per cent was recovered in the feces. There seems to be no indication for intravenous therapy at the present time, since streptomycin is readily absorbed into the blood stream after intramuscular injection.

When streptomycin is injected intramuscularly at the rate of 0.125 Gm. every three hours, it is distributed rapidly to the urine and more slowly to pleural and peritoneal fluids. After administration at this rate for twenty-four hours, streptomycin levels in pleural and peritoneal fluids are roughly equivalent to the levels observed in the blood. In the bile, somewhat lower levels are reached, and in the spinal fluid, little of the antibiotic is found in the absence of meningeal inflammation. The usual body fluid levels obtained following the administration of 1.0 Gm. per day in eight divided doses intramuscularly are shown in Fig. 1. Some of the variations observed are shown by the dotted portions of the graphic representations. It would seem, therefore, from our studies and others, that streptomycin is a drug of relatively low toxicity, not likely to produce late injury except after prolonged administration, and that it is widely distributed in various body fluids other than the spinal fluid after parenteral administration.

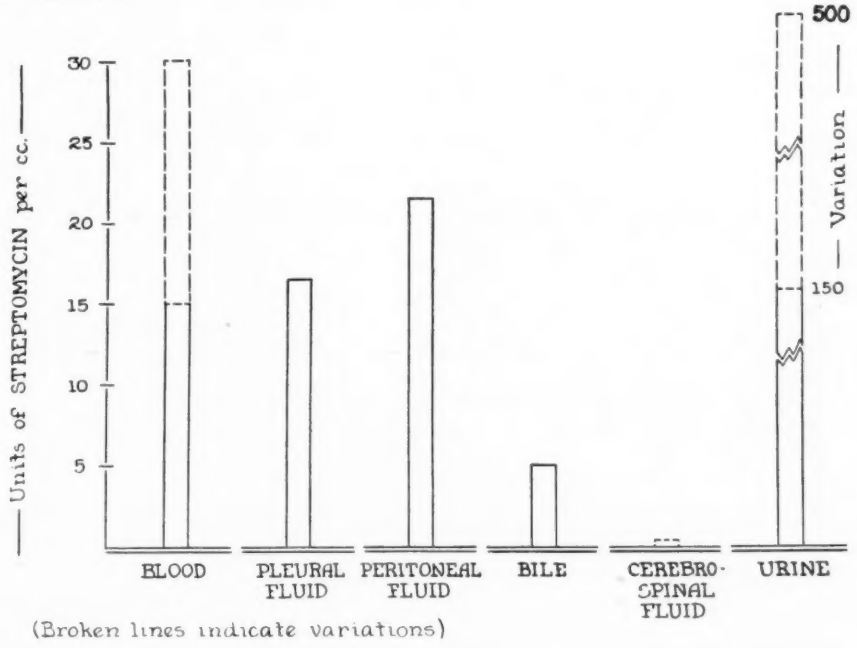

Fig. 1.—Distribution of streptomycin following the injection of 125,000 units intramuscularly every three hours for twenty-four hours.

From the surgical standpoint, we have been interested in four fields of usefulness: urinary tract infections, experimental peritonitis, wound infection, and the prophylactic preparation of patients for operations on the large bowel.

Streptomycin has been used to treat patients whose urinary tract infections have been resistant to penicillin and the sulfonamides. Eighteen of the patients had one or more of the following lesions of the genitourinary tract: prostatic hypertrophy with obstruction, carcinoma, diverticulum, calculus, cystostomy,

ureterostomy, or nephrostomy. The remaining six patients had no anatomic lesions of the genitourinary tract. The entire group of twenty-four patients received 1.0 Gm. of streptomycin divided into eight intramuscular doses each day for ten days. Fifty-eight per cent of all of the cases were relieved either symptomatically or bacteriologically, 21 per cent had an immediate response but relapsed while still under treatment, and 21 per cent failed to respond.

Two factors may play a part in the relapse of infection in patients while they are under streptomycin therapy. First, it is well known that the resistance of certain organisms to streptomycin can change very rapidly, especially when the concentration of streptomycin is relatively low. Second, in several patients with evidence of severe renal damage, very low urine streptomycin concentrations were found. Fig. 2 shows the course in a patient in which both of these factors were observed. Urinary concentration of streptomycin in this

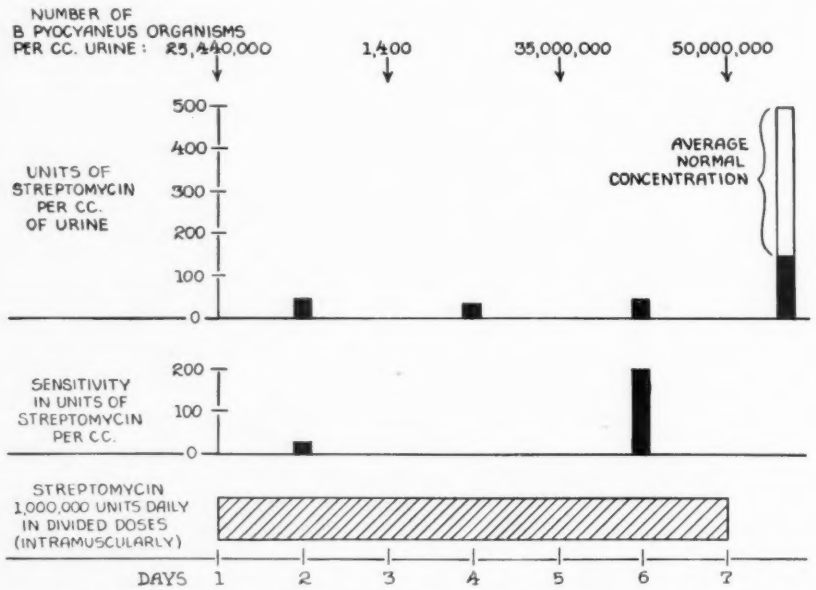

Fig. 2.—Effect of decreased renal function on streptomycin treatment of *B. pyocyaneus* urinary tract infection.

patient varied between 35 and 45 units per cubic centimeter, of urine instead of falling in the expected range of 150 to 500 units. The initial streptomycin sensitivity of the pyocyaneus organism was 35 units of streptomycin per cubic centimeter of agar. After receiving 1.0 Gm. of streptomycin daily for two days, the number of pyocyaneus organisms per cubic centimeter of urine fell from 25,000,000 to 1,400. On the fifth day of therapy, the number of organisms per cubic centimeter of urine was 35,000,000. On the sixth day of therapy the sensitivity of the organism was 200 units of streptomycin. It, therefore, seems probable that the very low streptomycin concentration in the urine of this patient was just sufficient to inhibit temporarily the growth of the organisms and at the same time low enough to allow the organism to increase its resistance to streptomycin.

The types of infection were, for the most part, mixed infections of gram-negative and gram-positive organisms. The types of infection and the associated urinary pathologic conditions of the patients were too varied to permit further analysis of this small group of urinary tract infections. The results simply stated are twofold: (1) that 58 per cent of the urinary tract infections which were resistant to several other types of therapy responded to streptomycin, and (2) that the best results were obtained in the patients who had no urinary tract disease apart from the infection. In this small series of urinary tract infections, streptomycin was more effective than penicillin, sulfonamides, or mandelic acid.

The fact that a great many of the patients with associated genitourinary tract lesions had recurrences does not reduce the bacteriologic significance of the results obtained. As long as a primary lesion continues to be present, the patient will be susceptible to recurrent infection. Streptomycin will often, however, produce a remission of the infection and thus prepare the patient for such manipulative or operative procedures as are deemed necessary.

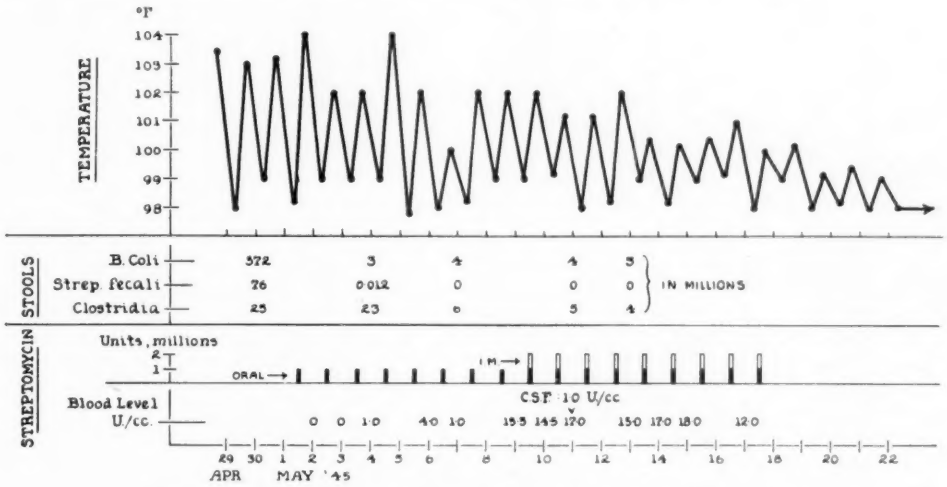

Fig. 3.—H. B., a white woman, aged 42 years; ulcerative colitis.

WOUND INFECTIONS

In the field of colon bacillus wound infection our results are not well enough controlled to have significance as yet. We have used the drug in a base of carbowax and propylene glycol in a concentration of 2,500 micrograms per cubic centimeter in several persistent infections near the anus with sufficiently prompt improvement to indicate a causal relationship.

ULCERATIVE COLITIS

In four cases of ulcerative colitis, the drug, administered orally or orally and parenterally, failed to arrest the disease. In acute exacerbations of the disease, however, it was followed by a lowering of the temperature, and at times it appeared to avert an early fatal outcome. Fig. 3 shows the temperature course and some of the bacteriologic findings in such a case.

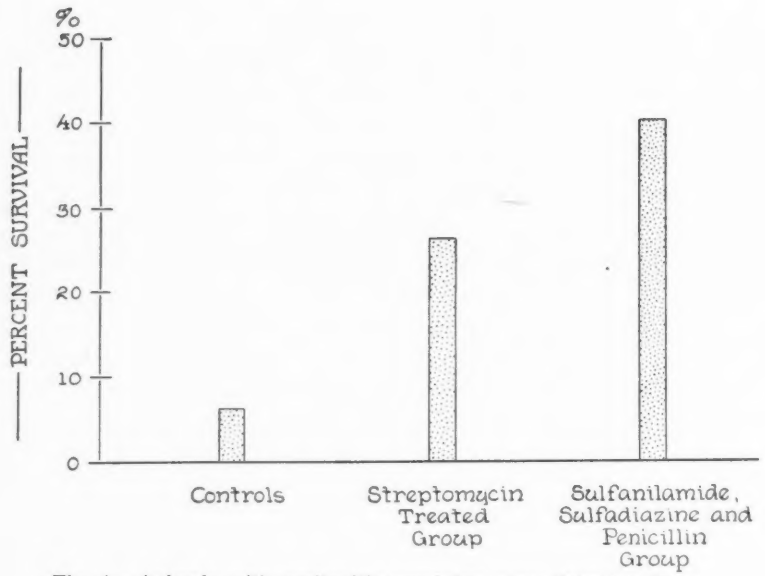

Fig. 4.—Animals with peritonitis surviving more than ten days.

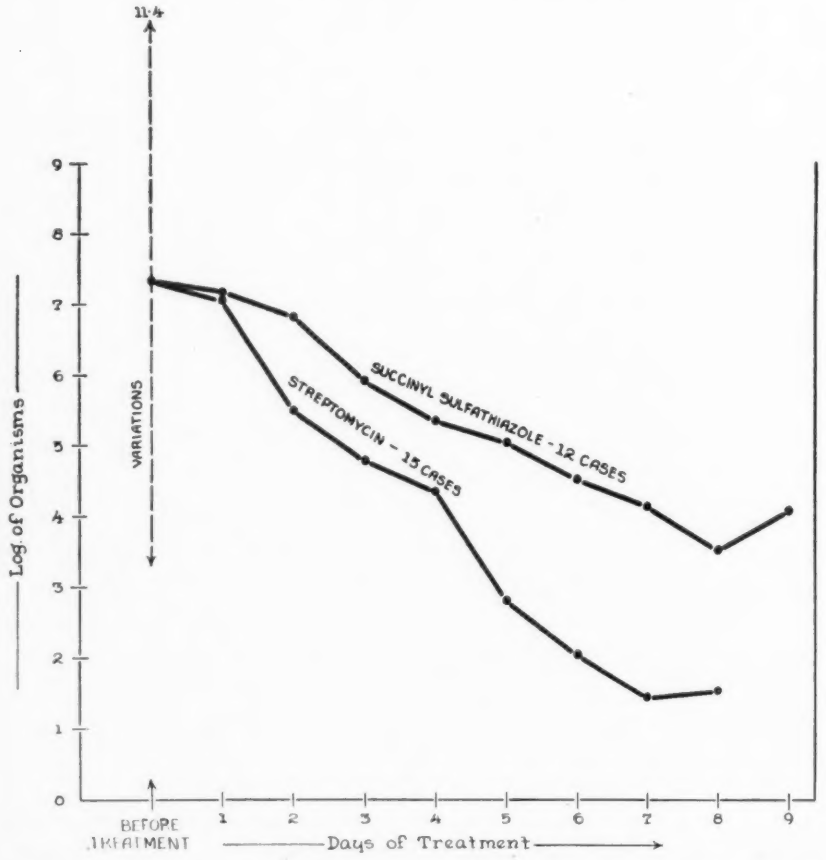

Fig. 5.—Effect of streptomycin and succinylsulfathiazole on the number of *B. coli* in the feces.

PERITONITIS

Theoretically, streptomycin would appear to be the ideal drug for chemotherapy in peritonitis, especially in the common mixed forms arising from the rupture of hollow viscera. The excellence of the results with sulfonamides and penicillin, however, makes one hesitate to change to a new drug without considerable experience with animals.

In a series of experiments recently reported, Murphy and associates[3] obtained seven ten-day survivals among ten dogs in which peritonitis was established by ligation of the appendix and its mesentery, the technique suggested by Bower and modified by Fauley and associates.[4] Three of ten controls survived.

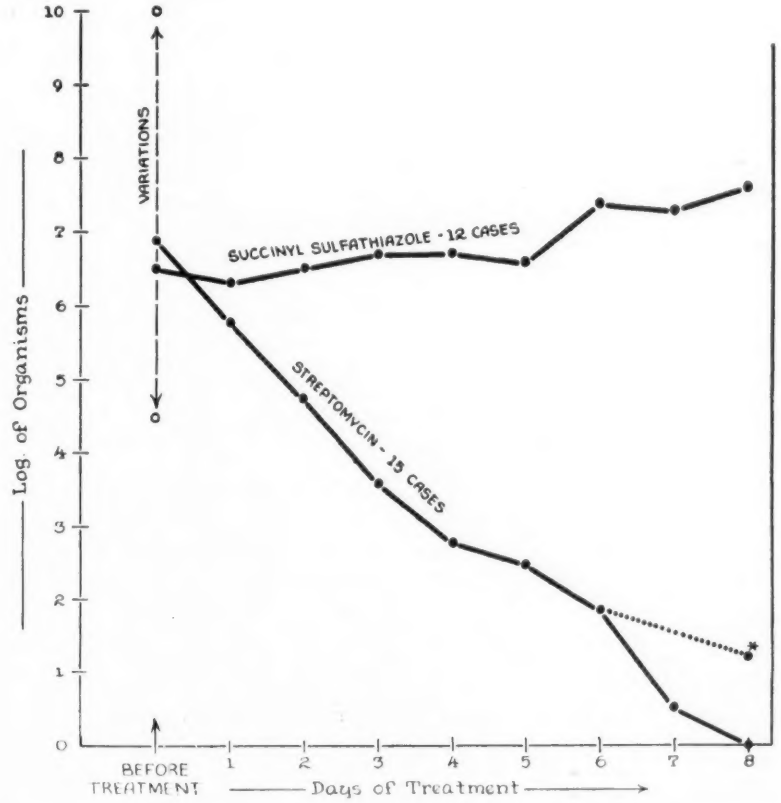

Fig. 6.—Effect of streptomycin and succinylsulfathiazole on the number of streptococcus fecalis organisms in the feces.

In order to get a more definitive infection in subsequent experiments, the Bower technique was modified by opening the appendix after its ligation, as suggested by Meleney and co-workers.[5] Three groups of fifteen animals each in which peritonitis had thus been produced were studied. The first group served as controls and received no special medication. They were allowed water immediately after operation and were allowed to eat on the first postoperative day.

The second group of animals received intramuscularly an amount of streptomycin equivalent to 16,666 micrograms for each kilogram of body weight

every four hours for eight days and then 25,000 micrograms per kilogram every eight hours for two days.

Treatment of the third group of animals was by local sulfanilamide crystals, 0.4 Gm., in the peritoneal cavity at the time of operation followed by parenteral penicillin, 60,000 units of calcium penicillin in a peanut oil-beeswax mixture every twelve hours intramuscularly, and sodium sulfadiazine, 0.65 Gm. intravenously every twelve hours for ten days. Of the control animals, 6.6 per cent survived the ten-day period; of the streptomycin-treated animals, 26.6 per cent survived; and of the sulfanilamide-penicillin-sulfadiazine group, 40 per cent survived.

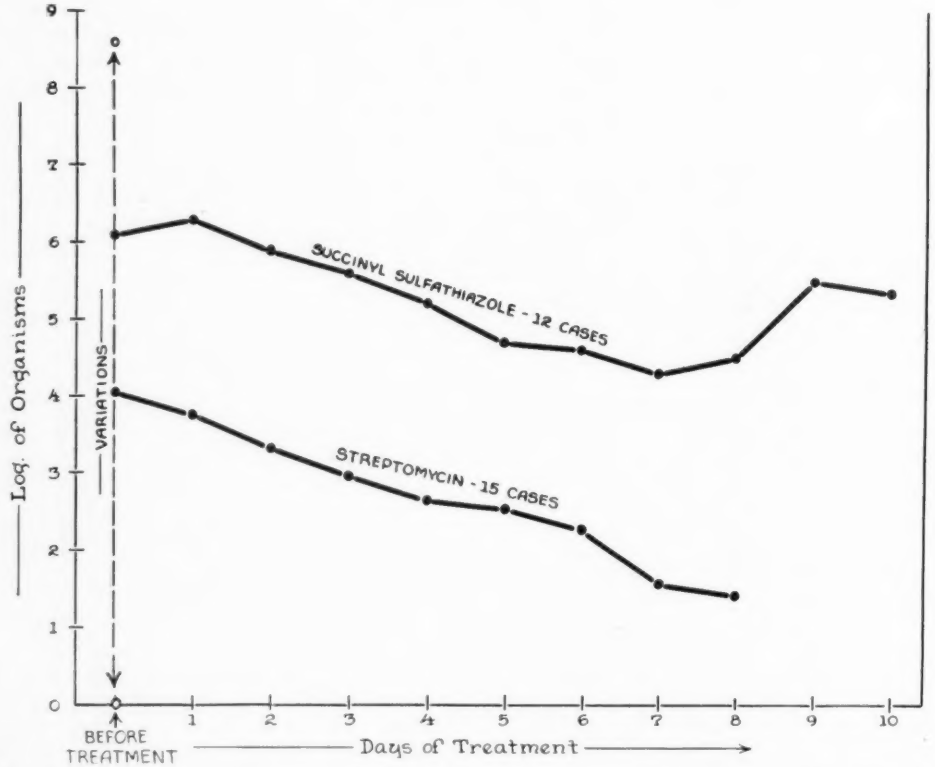

Fig. 7.—Effect of streptomycin and succinylsulfathiazole on number of clostridial organisms in feces.

On the basis of these experiments, we think one should not substitute streptomycin for the other chemotherapeutic agents in peritonitis until further study provides a sound basis for the change. Further experiments in which streptomycin is used as a supplement to other chemotherapeutic agents are in progress.

PROPHYLAXIS IN LARGE BOWEL SURGERY

Several drugs have been advocated in recent years to reduce the flora of the intestinal tract in preparation for surgery. Among these, succinylsulfathiazole is probably the best known. Streptomycin administered by the oral route is especially suitable for this purpose, and, in order to obtain a more

accurate evaluation, it was administered in doses of 1.0 Gm. per day to fifteen patients for periods of from six to ten days. Quantitative stool cultures were carried out by Miss Marjorie Wiley before treatment was started and at two-day intervals thereafter. By plating out stool suspensions on differential media, counts were obtained for the coliform group of organisms, *Streptococcus fecalis* and Clostridia. The results were compared with similar data obtained by Lockwood and Zintel previously with succinylsulfathiazole. With both drugs, occasional patients show marked deviations from the mean. The logarithms of the counts were plotted against time of drug administration and an average curve was drawn for each drug and each group of organisms. The relative effectiveness of succinylsulfathiazole and streptomycin on *Bacillus coli, Str. fecalis,* and the clostridial organisms is shown in Figs. 5, 6, and 7. The figures used are the average of the logarithms, not the logarithm of the averages. Streptomycin, even in the limited dosage employed, was much more effective than was succinylsulfathiazole.

SUMMARY AND CONCLUSIONS

Streptomycin is a drug of relatively low toxicity. It is widely distributed in body fluids, except spinal fluid, after parenteral administration, but apparently it does not readily cross the wall of the alimentary tract. Hence it should be given orally if it is to influence the flora of the feces.

It is effective in many urinary tract infections of both gram-negative and gram-positive organisms that have failed to respond to penicillin and a sulfonamide, but not in all. It has, perhaps, a special field of usefulness in infections due to *Bacillus proteus* and *Bacillus pyocyaneus.*

It has exerted a beneficial influence on the course of experimental peritonitis in dogs. The difference was statistically significant when combined with an earlier group of experiments in this laboratory. The therapeutic effect, however, was not as great as that observed with a combination of sulfonamides and penicillin.

Streptomycin appears to be a very effective agent in reducing the bacterial count in the stools. It reduced the coliform organisms to a greater degree than succinylsulfathiazole and reduced the *Str. fecalis* and Clostridia to a much greater extent.

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17-KETOSTEROIDS IN THE DIAGNOSIS OF ADRENAL TUMORS

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CLINICAL syndromes involving masculinizing symptoms have long been recognized, Thomas Cook in 1765 being the first to describe a child with changes probably due to excess androgens. Before 1932 there was great confusion over the etiologic factors involved in these syndromes. Suggested causative agents included adrenal tumors, ovarian tumors, thymic tumors, and other vague endocrine disorders.

Bullock and Sequeira in 1905 published a series of eleven cases of masculinization in women caused by adrenal cortical lesions, and in 1912 Gallais introduced the term "adrenogenital syndrome."

In 1932 Cushing recorded a number of cases of masculinization in which basophil adenomas of the anterior pituitary had been demonstrated. This syndrome is characterized by rapid, plethoric, painful obesity of the trunk and head, acrocyanosis with purplish striae atrophicae, hypertrichosis, osteoporosis, polycythemia, hypertension, insulin-resistant diabetes, and muscular weakness.

Frequently no definite lesion of other endocrine glands is demonstrable, but the adrenals are usually enlarged and may contain small adenomas which Cushing regarded as secondary. That a very similar syndrome may be caused by tumor or hyperplasia of the adrenal cortex also has been definitely established, and in these cases there is an excessive amount of 17-ketosteroids demonstrable in the urine. At present it is thought that both pituitary and adrenal mechanisms may be involved, and there is no general agreement as to which is primary.

With the separation of the Cushing type of syndrome, there remains another clinical type characterized largely by masculinizing changes without the "metabolic" changes also present in Cushing's syndrome. In this so-called adrenogenital syndrome the patients, usually women, show hypertrophy of the clitoris, hirsutism, increase in musculature, deepening of voice, and irregularity or cessation of menses without the other changes of Cushing's syndrome. Etiologic factors have been shown to include ovarian tumors and adrenal cortical neoplasms.

There also appear to be many patients in whom the Cushing syndrome and adrenogenital syndrome are mixed in varying proportions, and it may be postulated that there are many degrees of combinations of "metabolic" factors and androgenic factors. The origin of the defect in many cases of pseudohermaphroditism is not clear, and there are many patients with simple hirsutism in whom no endocrine disorders are demonstrable.

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The differential diagnosis of the etiologic factors in these syndromes on clinical grounds alone is difficult. Roentgenograms of the skull, perirenal air insufflation or pyelograms may be very helpful, and a tumor of the adrenal or ovary at times may be palpable. The recent evidence brought forth by Crooke and Callow[7, 8] that the adrenal cortical tumor group may be differentiated by estimation of the greatly increased urinary androgens in these cases thus becomes of great significance.

The urinary 17-ketosteroids apparently are excretory transformation products of certain adrenal cortical steroid hormones and of testicular steroid hormones, and their output may be considered proportional to the combined secretory activity of these glands. Indirectly they also may give information regarding the anterior pituitary and thyroid glands because of the influence of the pituitary and thyroid hormones upon the adrenals and testes. In most cases, abnormally high rates of excretion are associated with adrenal cortical tumors or hyperplasia and with interstitial cell testicular tumors. Testicular tumor usually can be differentiated by the abnormal size of the involved testis.

The output of 17-ketosteroids in normal individuals has been shown in the Gynecology Endocrine Laboratory in this hospital by the method of Robbie and Gibson[22] to be as follows: adult women, 2.7 to 8.1 mg. per twenty-four hours; adult men, 3.4 to 15.0 mg. per twenty-four hours. According to Talbot and Butler,[25] children from 4 to 7 years of age excrete an average of 1.3 mg. per day; 7 to 12 years, 4.0 mg.; and 12 to 15 years, 8.2 mg. per day.

Estimation of the total 17-ketosteroids thus may be of great value in differentiating adrenal cortical lesions from pituitary and ovarian and other disorders, but it does not distinguish adrenal cortical hyperplasia from adrenal cortical carcinoma, both of which have excessive androgen production. However, it has been shown that the total 17-ketosteroid output can be separated into alpha and beta fractions, and there is evidence that whereas the alpha ketosteroids are produced by both the adrenals and testes, the beta ketosteroids arise only from the adrenal cortex.

Various workers have shown that normally the beta ketosteroid fraction comprises only about 5 to 15 per cent of the total 17-ketosteroid output, but that in adrenal cortical carcinoma the beta ketosteroid fraction becomes markedly elevated.[2, 23, 24] Thus, the fractionation of the total 17-ketosteroids gives important information which may enable the clinician to differentiate adrenal cortical hyperplasia from adrenal cortical carcinoma. Cushing's syndrome without adrenal tumor is associated with normal or only slightly elevated 17-ketosteroid excretion without increase in the beta fraction.

A survey of the literature reveals less than thirty-five cases of adrenal cortical tumor in which the total 17-ketosteroid output has been determined, and fractionation into alpha and beta portions has been performed in only a very few. We wish to report three proved cases of adrenal cortical carcinoma associated with markedly elevated total 17-ketosteroid excretion in which fractionation into alpha and beta portions has been of definite value in the differential diagnosis.

TABLE I. SUMMARY OF REPORTED 17-KETOSTEROID EXCRETION IN PATIENTS WITH PROVED ADRENAL TUMORS

	AUTHOR	SEX	AGE	MG. PER DAY (TOTAL 17-KS)	ALPHA 17-KS	BETA 17-KS	CLINICAL	DISPOSITION	FOLLOW-UP
1	Crooke and Callow[8]	M	25	40 to 64		30	Headaches, obesity, plethora, striae, acne; no glycosuria or hypertension; perirenal air, left adrenal tumor	Excision of tumor, carcinoma of adrenal cortex	Postop. 17-KS, 1.9 to 8.3 mg.
2	Crooke and Callow[8]	F	6	126 to 288		120	Swelling of abdomen, pubic hair, large mass in left groin; obesity, acne, hirsutism, enlarged clitoris, hypertension, ascites	Death, autopsy, carcinoma of adrenal cortex	
3	Friedgood and Whidden[14]	F	–	45					
4	Friedgood and Whidden[14]	F	10	325			Hirsutism, masculine voice, acne, hypertension, polycythemia, acrocyanosis, striae, menstruation at age of 8, enlarged clitoris	Malignant adrenal cortical tumor removed at operation	
	Talbot et al.[23]	F	13	166	83	83			
5	Talbot et al.[23]	F	3	160	56	104	Large genitals and pubic hair, acne, increased musculature and size; mass over right kidney, increased osseous development	Excision of tumor, malignant; tumor of fetal adrenocortical origin	
6	Fraser et al.[12]	F	56	74			Weakness, hirsutism, baldness, dyspnea, back pain, florid face, acne, blood pressure 170/100, hyperglycemia, decalcification of spine	Autopsy: adrenal carcinoma, 1 kg.	
7	Fraser et al.[12]	F	36	19.9 (stored 5 yr.)			Hypertrichosis, furunculosis, kidney stones, obesity, decreased stature; headaches, deep voice, amenorrhea hyperglycemia, decalcification of spine, blood pressure 170/135	Malignant tumor on left, autopsy	
8	Fraser et al.[12]	F	3½	132 to 220, 176			Enlarged clitoris, pubic hair, acne, deep voice, body hair, bone age 10 yr.	Operation, encapsulated tumor of fetal adrenal cortical tissue, 110 Gm.	
9	Patterson et al.[20]	M	1	28 mg. per liter			Isosexual precocity		
10	Patterson et al.[20]	M	5	27			Isosexual precocity		
11	Patterson et al.[20]	F	Adult	173			Cushing's syndrome		
12	Patterson et al.[20]	F	34	270			Cushing's syndrome		
13	Talbot et al.[24]	F	56	74	51	16			
14	Anderson et al.[1]	F	25	215			Amenorrhea, abdominal swelling, slight hirsutism, x-ray, tumor, left kidney; death, pulmonary embolism	Autopsy: tumor of left adrenal, 1,480 Gm. carcinoma of adrenal cortex	
15	Baumann and Metzger[2]	F	25	2.3	2.3	0	3 wk. P.O. operation for adrenal cortical carcinoma		
				367	257	110	Recurrence of adrenal cortical carcinoma		
16	Callow and Crooke[7]	F	61	145 to 220			Weight gain, weakness, hirsutism, B.P.,	Carcinoma of left ad-	

16	Callow and Crooke[7]	F	61	145 to 220			Weight gain, weakness, hirsutism, B.P., 200/60; pyelogram, left kidney depressed (aged and very ill)	Carcinoma of left adrenal cortex excised, death 3 mo. later	
17	Callow and Crooke[7]	F	26	25 to 107			Scanty, irregular menstruation, hirsutism	Right adrenal cortical adenoma removed, 1938; recent perirenal air, left adrenal tumor	25 to 65 mg., 1938; 108 mg., 1942
18	Callow and Crooke[7]	F	41	76 to 78			Virilism, wasting, hirsutism, irregular menstruation	Left adrenal cortical carcinoma	
19	Callow and Crooke[7]	F	38	52 to 54			Basophilism with right adrenal cortical carcinoma		
20	Hirschmann[17]	M	7	275 to 420					
21	Engstrom et al.[10]	M	1¼	2.8					
22	Engstrom et al.[10]	F	1¼	3.0					
23	Engstrom et al.[10]	F	63	45.6					
24	Engstrom et al.[10]	F	16	54.6					
25	Engstrom et al.[10]	F	25	131.0					
26	Engstrom et al.[10]	F	3½	170.0					
27	Engstrom et al.[10]	F	21	240.0					
28	Engstrom et al.[10]	F	45	857.0					
29	Warren[26]	F	54	83			Melancholia and manic depression; florid, hirsutism, abdominal swelling	Operation, adrenal cortical carcinoma; P.O. pneumonia	
30	Warren[26]	F	42	690			Hirsutism and weight gain, headaches, palpitation, skin dry, hair falling out	Operation, carcinoma of right adrenal cortex; death soon after operation	
31	Warren[26]	F	49	269				Removal of large tumor of adrenal cortex	187 mg. 24 hr. P.O.; 7.7 mg. 10 days P.O.
32	Warren[26]	F	40	126			Abdominal swelling, hirsutism, obesity	Operation, removal of carcinoma of adrenal cortex	
33	Johnson and Nesbit	F	2	78.5 21.0*	15.7†	62.3‡	Pubic hair, enlarged clitoris, x-ray, right kidney depressed	Excision of right adrenal cortical carcinoma	0.9 mg. P.O., clinical recovery
34	Johnson and Nesbit	F	31	75	19.7†	55.3‡	Oligomenorrhea, weight gain, acne, hirsutism, loss of libido; pyelograms, calcified mass above right kidney	Excision of right adrenal cortical carcinoma	Clinical recovery; 2.8 mg. 10 days P.O.; 2.98 to 6.6 mg. during next 12 mo.
35	Johnson and Nesbit	M	43	86	36.6†	49.4‡	Previous nephrectomy for left "hypernephroma"; sections showed adrenal carcinoma, now has large left flank mass and weight loss	X-ray therapy	25.4 mg. after x-ray; 102 mg. 2 mo. later with metastasis

*Probable incomplete twenty-four hour urine specimen.
†Determined by method described by Frame.[11]
‡By difference between total and alpha ketosteroid fractions.

CASE REPORTS

CASE 1.—E. D., a 31-year-old married white woman, had a six months' history of loss of libido, scanty menses, fifteen pound weight gain, acne, and hypertrichosis. A vague mass was not easily palpable in the right upper quadrant. There was no hypertension. Pyelograms revealed a faintly calcified mass above the right kidney. Urinalysis was negative. Findings were negative in skull and chest roentgenograms. Basal metabolic rate was –2 per cent. Blood calcium, phosphorus, and alkaline phosphatase were normal. Physical examination, including the genitals, was otherwise negative; 17-ketosteroids: 75 mg. per day (alpha 17-ketosteroids, 19.7 mg.; beta, 55.3 mg.).

On Jan. 13, 1945, the right adrenal gland was explored through a right flank incision, and a well-encapsulated, grapefruit-sized tumor weighing 660 Gm. was removed. The postoperative course was uneventful without evidence of shock or adrenal insufficiency. Pathologically the tumor was a poorly differentiated adrenal cortical carcinoma with much necrosis. Ten days postoperatively, total 17-ketosteroids excretion was 3.8 mg. per day.

FIG. 1 (Case 1).—Married woman, 31 years of age, before and six months after removal of right adrenal cortical carcinoma. Patient had a six months' history of loss of libido, scanty menses, hirsutism, acne, and weight gain. The operation was followed by complete clinical recovery and normal 17-ketosteroid excretion.

The patient was seen at regular intervals for a period of one year postoperatively, during which time she showed progressive improvement with return of menses, libido, and general well-being, and loss of hypertrichosis and acne. Four 17-ketosteroid determinations during this period ranged from 2.98 to 6.6 mg. per day, all within normal limits. There was no evidence of metastasis.

CASE 2.—M. S., a 2-year-old white girl, was noted at about 1 year of age to have an unusual growth of pigmented pubic hair which gradually increased. She was said always to have had a large clitoris which apparently had not changed during this time. There had been no menstrual flow. Examination revealed a normal child in all other respects. No

Fig. 2.

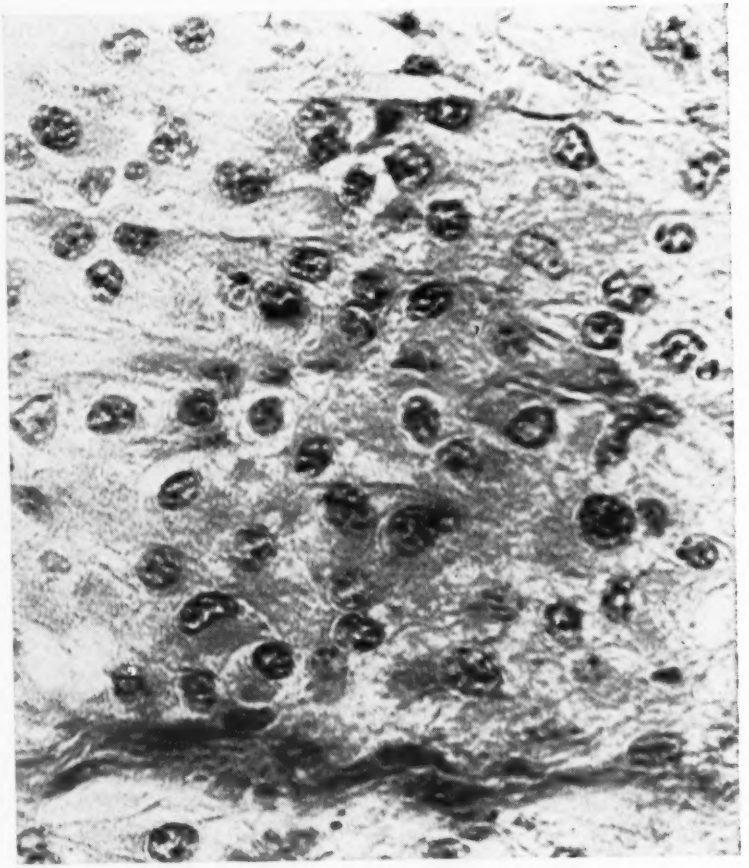

Fig. 3.

Fig. 2 (Case 1).—Adrenal cortical carcinoma removed from right adrenal gland. The tumor was solid, well encapsulated, and weighed 660 Gm.

Fig. 3 (Case 1).—Photomicrograph showing poorly differentiated adrenal cortical carcinoma removed (hematoxylin and eosin, ×140).

abdominal tumor was palpable. One urinalysis showed 2+ glycosuria, but all subsequent urinalyses were negative. Blood sugar was 81 mg. per cent. Blood pressure was normal. Roentgenograms showed bone age to be within normal limits. Findings from chest and abdominal scout films were negative. Excretory urograms demonstrated the presence of a right adrenal tumor depressing the right kidney; 17-ketosteroids: 78.5 mg. per day (alpha 17-ketosteroids, 15.7 mg.; beta, 62.3 mg.). One total 17-ketosteroid determination was 21.0 mg. per day, but this lower value was attributed to failure to obtain a complete twenty-four-hour urine specimen. Estrogens were not measurable.

On April 11, 1945, the right adrenal gland was explored through a right flank incision, and a well-encapsulated 6 by 5 cm. rounded, solid tumor weighing 72 Gm. was removed. The postoperative course was uneventful without signs of adrenal insufficiency. Pathologically the tumor was an adrenal cortical adenoma undergoing carcinomatous degeneration with numerous hyperchromatic nuclei and neoplastic giant cells. Ten days postoperatively, total 17-ketosteroid excretion was 0.9 mg. per day.

Fig. 4 (Case 2).—White girl, 2 years of age, with excessive pubic hair before removal of right adrenal cortical carcinoma. After operation the child showed clinical improvement and normal 17-ketosteroid excretion, but the pubic hair regressed only moderately.

Six months postoperatively the child showed clinical improvement with increase in well-being and normal development. Pubic hair regressed only moderately. There was no evidence of metastasis. Total 17-ketosteroid excretion six months postoperatively remained at 0.9 mg. per day.

CASE 3.—H. W., a 43-year-old white man, noted the onset ten months previously of dull pain radiating into the left inguinal region, followed by ease of fatigue, loss of appetite, and loss of weight. A left flank mass became palpable and pyelograms were suggestive of

Fig. 5.

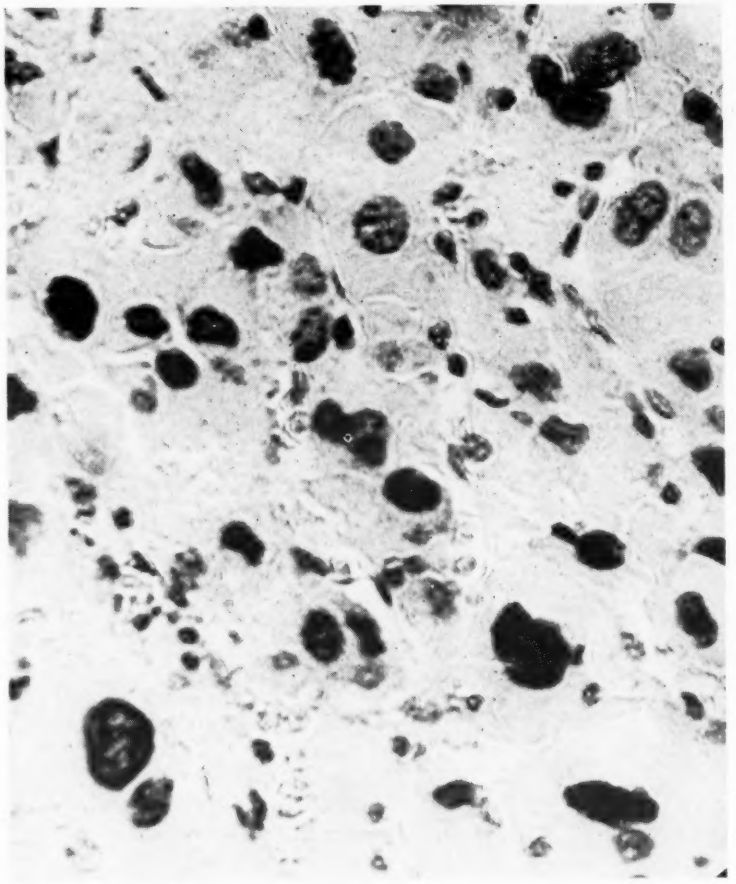

Fig. 6.

Fig. 5 (Case 2).—Adrenal cortical adenoma with carcinomatous degeneration removed. The tumor was solid, well encapsulated, and weighed 72 Gm.

Fig. 6 (Case 2).—Photomicrograph showing adrenal cortical adenoma with carcinomatous degeneration removed. There are numerous hyperchromatic nuclei and neoplastic giant cells (hematoxylin and eosin, ×140).

neoplasm. Left nephrectomy was performed in another hospital, and draining sinuses persisted postoperatively until his admission to University Hospital. Symptoms were unrelieved and abdominal pains increased. There was no history of masculinization or feminization. The emaciated patient entered University Hospital in February, 1945, and pathologic examination of sections from the nephrectomy interpreted them as adrenal cortical carcinoma. A large irregular mass was palpable in the left upper quadrant. Blood pressure was normal. Chest and spine roentgenograms were negative; 17-ketosteroids: 86 mg. per day (alpha 17-ketosteroids, 36.6 mg.; beta, 49.4 mg.). Urinalysis was negative.

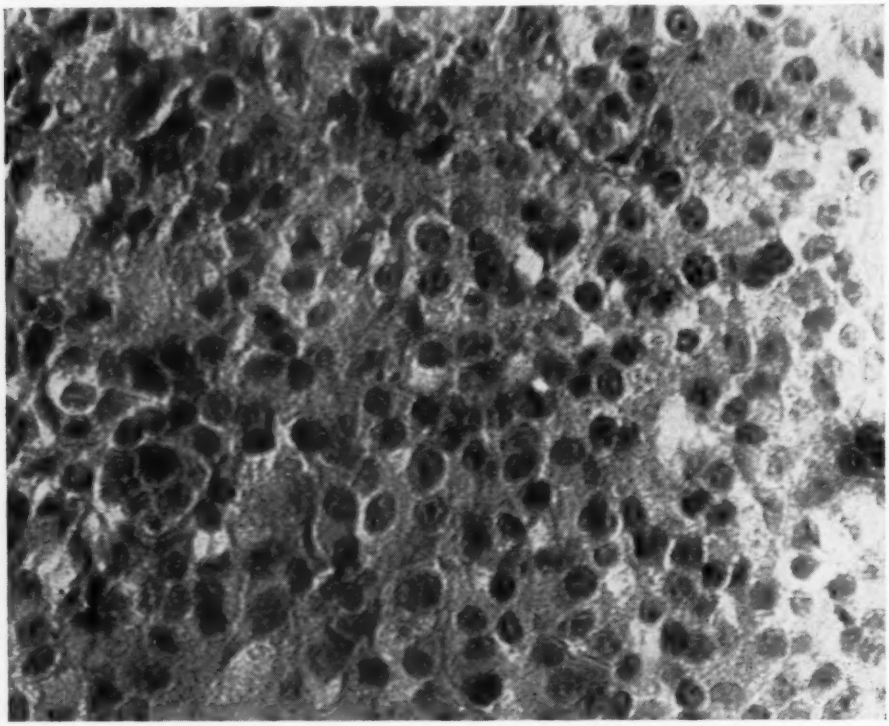

Fig. 7 (Case 3).—Photomicrograph of poorly differentiated adrenal cortical carcinoma in 43-year-old-white man. The diagnosis was made from tissue removed at previous nephrectomy and there was widespread extension when he was seen for the first time at University Hospital (hematoxylin and eosin ×140).

The patient was given a course of roentgen therapy, and total 17-ketosteroid excretion following this was 25.4 mg. per day. He returned home and was improved for a short time, but this was followed by development of right flank pain, weakness, loss of appetite, right pleuritic pain, and painful breasts. On readmission two months after discharge, examination revealed cachexia, large right flank tumor, marked decrease in size of original left flank tumor, and right pleural effusion. Urinalysis was negative. Total 17-ketosteroid output had risen to 102 mg. per day. Urinary estrogen was elevated to 10 R.U. per day (normal is less than 5 R.U. per day). Further irradiation was deemed inadvisable, and he was discharged for terminal care.

CONCLUSIONS

1. The determination of the urinary 17-ketosteroid excretion is of differential diagnostic value in masculinizing syndromes.

2. An elevated total 17-ketosteroid excretion with an abnormal increase in the beta fraction is strongly suggestive of adrenal cortical carcinoma.

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RETROPERITONEAL TERATOMA

Successfully Removed From a Fifteen-Month-Old Negro Girl

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BENIGN retroperitoneal neoplasms with the structure of a teratoma are exceedingly rare, particularly in children. A detailed review of "retroperitoneal mesodermal mixed tumors" in general has just been published by Lähteenmäki.[1] Twenty-three cases of "retroperitoneal teratoid tumors" in infancy and childhood were tabulated by Arnheim.[2] Eighteen of these occurred in children under the age of 2 years. According to Arnheim, his patient, a female infant 3 months old, was the fourth in this age group in whom the tumor was successfully removed. Our patient, a 15-month-old Negro girl, is, presumably, the fifth in whom a large retroperitoneal growth, structurally a teratoma, was surgically removed.

REPORT OF CASE

A. N. R., a 15-month-old Negro girl, was admitted to the University of Oklahoma Hospitals, Oct. 15, 1943, with the complaint of progressive enlargement of the abdomen and dyspnea. According to the mother, enlargement of the right side of the abdomen was first noted when the child was 6 months old and for the past three months the entire abdomen had been enlarged. No irregularity of bowel habit was noted. The mother said that the child was small at birth; the exact weight was unknown to her. The child was breast fed for the first six months, during which time she vomited frequently. Eight brothers and sisters were in good health and without known malformations. On admission the child was poorly nourished with the skin dry, loose, and wrinkled; she weighed 20 pounds, 4 ounces. Rectal temperature was 99.6° F.; the pulse rate was 140; the respiration was costal, labored, and 46 per minute. There was marked uniform distention of the abdomen. The presence of fluid could be demonstrated and a large abdominal mass arising apparently from the posterior wall was indistinctly palpable.

Urinalysis was essentially negative. The red blood cell count was 4,500,000; the hemoglobin content was 12.5 Gm.; the white blood cell count was 7,600, with polymorphonuclears 36, and lymphocytes, 64 per cent. Similar results were obtained on Nov. 1, Nov. 15, and Dec. 8, 1943. The Kolmer-Wassermann test of the blood was negative. A tuberculin test was negative. Roentgenographic examination of the chest on October 19 revealed marked abdominal distention with elevation of the diaphragm on both sides deforming the cardiac shadow and compressing the right lung. No abnormal tissue shadow was demonstrable. A gastrointestinal series, October 23, disclosed upward displacement of the stomach. At five hours there was gastric residue with barium in the terminal ileum. On October 25, abdominal paracentesis yielded 1,850 c.c. of clear straw-colored fluid. Examination for acid-fast organisms proved negative. After removal of the fluid, a large indefinitely delineated mass could be felt on the right side of the abdomen apparently fixed to the posterior abdominal wall.

Peritoneoscopic examination on November 4 disclosed no adhesions, no nodules, and no evidence of any inflammatory lesions. The liver, gall bladder, stomach, small intestine, urinary bladder, uterus, Fallopian tubes, and ovaries were visualized and appeared as usual.

Examination with barium enema on November 8 disclosed no intrinsic lesions in the colon but an anterior displacement of the right side of the colon and hepatic flexure by a retro-

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peritoneal mass. Intravenous pyelograms visualized the calices and pelvis of the left kidney and they appeared normal. A small amount of dye could be seen in the right kidney, obscured by a soft tissue mass. It was surmised that the tumor involved the right kidney.

Roentgen irradiation was given over a fourteen-day period (November 15 to 29) using anterior, posterior, and lateral portals with the following factors: 18 ma., 200 kv., distance 50 cm., Thoraeus filter. A total of 1,200 r. was given to each portal, making the total dose in air 3,600 r. There was no demonstrable effect.

Retrograde pyelograms taken Jan. 4, 1944, revealed the usual configuration of the calices and pelvis of the left kidney. The right kidney was displaced downward and outward with the pelvis elongated, suggestive of extrinsic pressure with slight distortion of the calices. The idea of a neoplasm arising from the right kidney was abandoned.

On January 12 a laparotomy was performed and a retroperitoneal mass, about 22 by 18 by 16 cm., was located. The peritoneal surfaces were smooth and glistening and there were no adhesions. The ascending colon and hepatic flexure were displaced medially as well as the pylorus and duodenum. The mass was adherent to the posterior surface of the liver and distally to the right kidney which was pushed into the iliac fossa. Medially it extended to the hilus of the left kidney. The mass was not adherent to any of the pelvic structures. There were several cystic areas on the anterior surface. From one of these, 40 c.c. of clear colorless fluid were obtained. In the course of the operation, another cystic area was ruptured on the posterior surface. Removal of the mass was accomplished through a longitudinal incision in the parietal peritoneum, by dissecting away the ileocecal region of the gut and separating the mass from its upper, lower, and dorsal connections. The blood supply originated from the dorsal aspect, apparently from the lumbar arteries, and also from the region of the liver where adhesions were dense. Sulfanilamide crystals (3 Gm.) were placed at the site of the tumor and the wound was closed, leaving a soft rubber drain brought out through a subcostal stab wound. The postoperative course was fairly uneventful and the patient was discharged from the hospital February 11, four weeks after the operation. When seen March 22, 1944, she was in good health, and she has been developing normally since.

The specimen removed was an oval, somewhat nodular, fairly well-encapsulated mass measuring 15 by 12 by 8 cm. (Fig. 1). One surface was smooth, pale gray yellow, and glistening. The opposite surface was ragged and mottled gray yellow and brown. A flap of tissue 11 by 9 cm. and 0.5 to 1 cm. thick was attached to one pole and a similar flap 11 by 7 cm. to the opposite pole. On the cut surfaces (Fig. 2) a capsule 0.1 to 0.3 cm. thick surrounded the mass composed mostly of adipose tissue. Occasional spaces from 0.5 to 3 cm. in diameter were filled with soft yellow or transparent jellylike material. Elsewhere, an oval field, 2 by 1.3 cm., of cartilaginous tissue was seen and a triangular area, 1 by 1 cm., of osseous tissue. Microscopically the thin portions of the cyst wall were composed of a broad zone of adipose tissue lobules and a narrow zone of hyalinizing fibrous connective tissue without an epithelial lining. The bulk of the mass was made up of lobules of adipose tissue with delicate or broad septa. The cartilaginous area imitated the structure of hyaline cartilage with the cells unevenly distributed in a homogeneous pink-lavender stained ground substance. The cells were single or in small groups within halolike spaces. Perichondrium separated the cartilage from the adipose tissue. The osseous area was bordered, partly by cartilage. Bony lamellae with discernible Haversian systems enclosed marrow spaces containing adipose tissue cells and groups and strands of marrow cells (Fig. 3). Within the adipose tissue, separated by a broad zone of collagenous fibers, there were delicate nerve fibrils with round or elongated cell nuclei in a cytoplasm which faded into the fibrils (Fig. 4). Within the adipose tissue, elsewhere, there was a cavity lined by a delicate layer of stratified squamous epithelium with three to five rows of cell nuclei and shreds of keratin on the surface. In the corium there were hair follicles and sebaceous glands opened into the hair follicles. There were also some sweat glands (Fig. 5). In preparations from the cystic fields, various-sized spaces were lined by tall columnar cells with light-stained cytoplasm and basally placed nuclei. Infoldings were frequent in some of the lumina. The spaces were separated by broad septa. Other small lumina lined by flat cells connected with the large lumina. Again

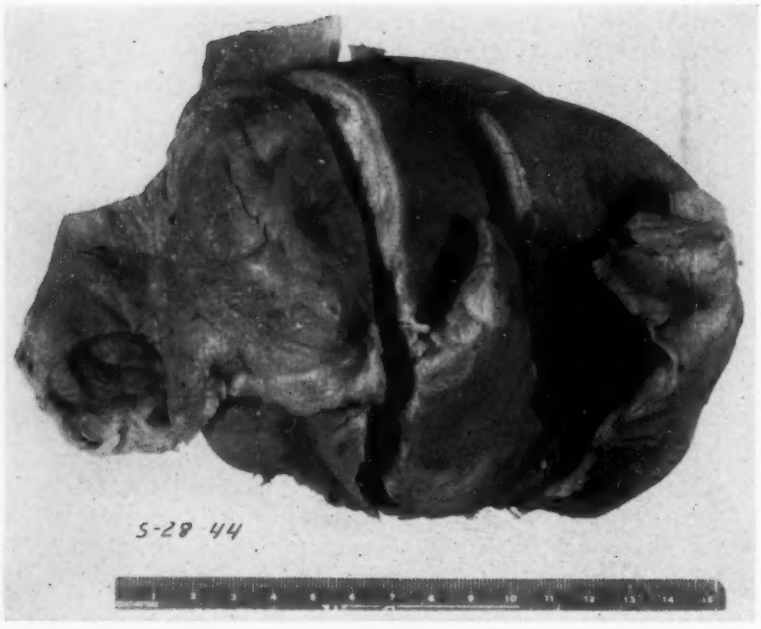

Fig. 1.

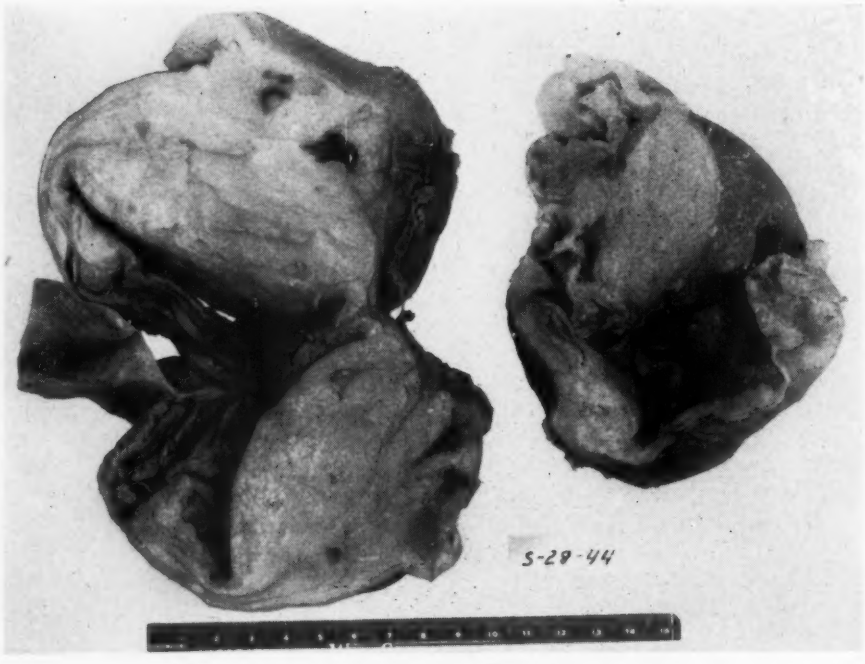

Fig. 2.

Figs. 1 and 2.—The appearance externally and on the cut surfaces of a retroperitoneal teratoma.

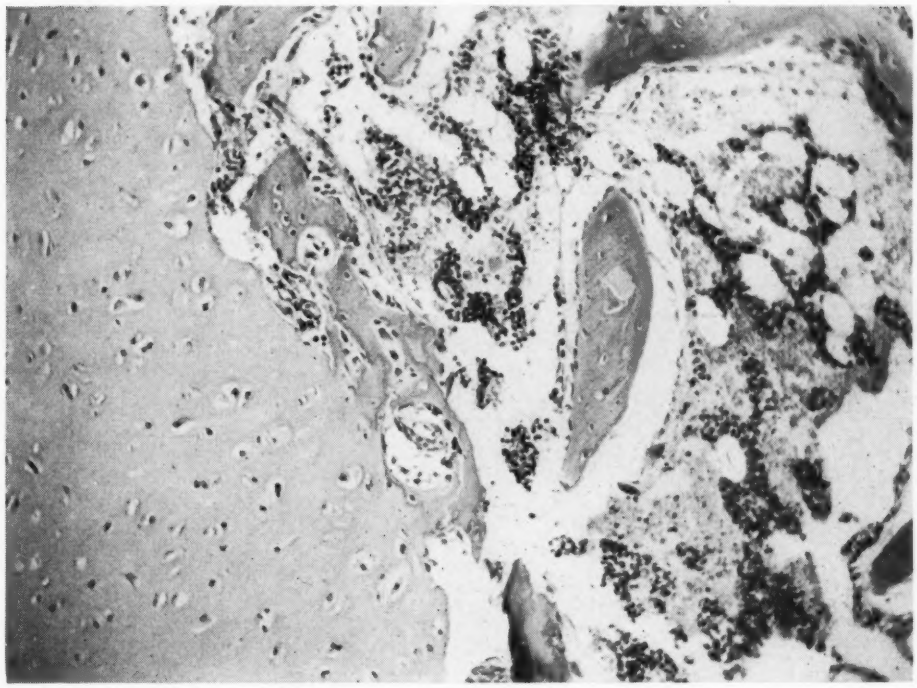

Fig. 3.—Microscopic appearance of the osseous area bordered by cartilage. Bony lamellae enclose marrow spaces containing adipose tissue cells and groups and strands of marrow cells (×150).

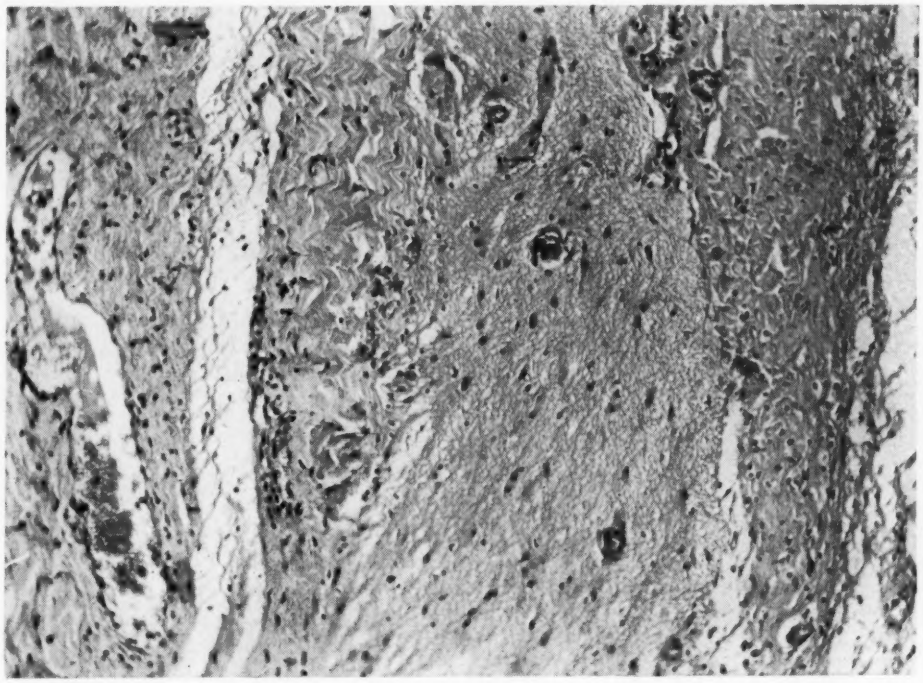

Fig. 4.—Delicate nerve fibrils with round or elongated cell nuclei in a cytoplasm fading into the fibrils (×150).

Fig. 5.—The lumen of a cavity lined by stratified squamous epithelium with hair follicles, sebaceous glands, and sweat glands in the corium (×150).

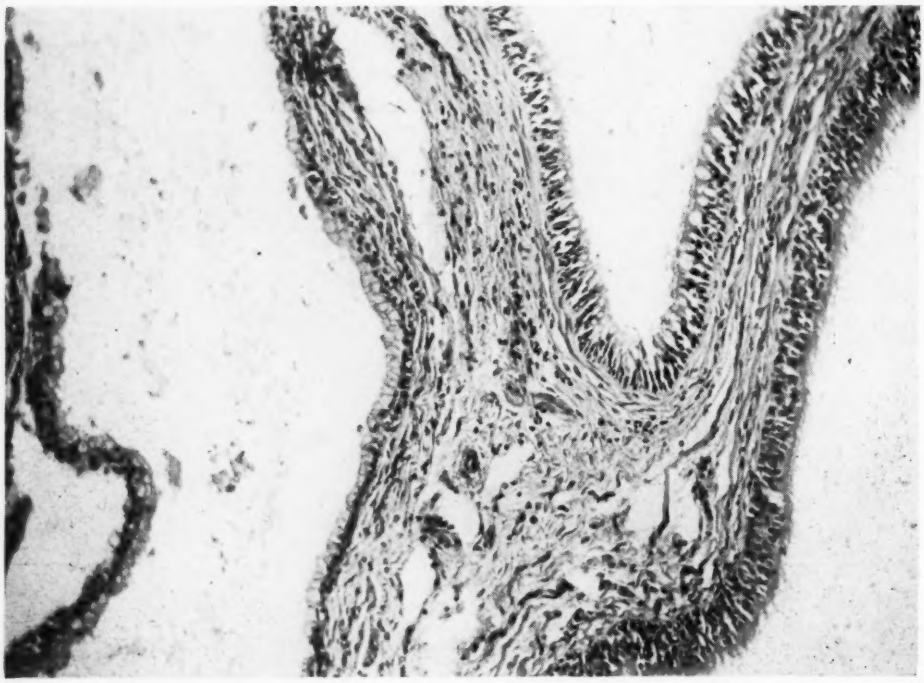

Fig. 6.—Spaces lined by columnar cells with light-stained cytoplasm and basally placed nuclei. One lumen is lined by ciliated columnar epithelium with several rows of reserve cells (×150).

other spaces contained a pink-stained amorphous material and the lining cells were flat or absent. One lumen was lined by ciliated columnar epithelium with several rows of reserve cells (Fig. 6). The line between the epithelium and subjacent connective tissue was usually straight.

COMMENT

It seems fairly clear that this teratoma arose from an embryonal anlage within the retroperitoneal space. The growth contained elements of skin and of nervous tissue, hyaline cartilage, osseous tissue with marrow spaces containing red marrow, adipose tissue and lumina lined by tall columnar cells. Judging from the histologic structure, the separation of the anlage must have occurred while the component cells still had the capacity to differentiate into tissues of all three of the germ layers. The benign character of the growth is obvious. Since it possessed, however, the same growth potentialities as the individual, progressive increase of the tissue elements proportionate with the growth of the individual would have occurred. Removal of the growth prevented further interference with the function and development of the adjacent viscera and of the individual as a whole.

SUMMARY

The clinical history is presented of a 15-month-old Negro girl with a large retroperitoneal teratoma. The growth was successfully removed and the patient is living and well two years after operation. This is believed to be the fifth recorded case in infancy or childhood in which a retroperitoneal teratoma has been successfully removed.

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DELAYED SUTURE OF WAR WOUNDS

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DELAYED wound closure was, with the exception of débridement, the operation most frequently performed in military surgery of World War II. Its importance, therefore, in hastening convalescence and expediting the return of the wounded soldier to duty cannot be overemphasized. This report deals with an analysis of 966 wounds, occurring in 315 patients, in which a delayed closure was performed. These patients were treated in a general hospital in Italy from November, 1943, through May, 1945. The cases herein presented include all of the wounds secondarily closed on one general surgical ward in this hospital. In addition to the general surgical type of patient, there were also upon this ward the maxillofacial and plastic cases and a considerable number of chest cases. Very few of the cases in the first two categories required this procedure, the greater portion of the face wounds having been closed in the forward hospitals; whereas, in many of the chest cases, delayed closures were required. In addition to the wounds presented herein, there were numerous wounds in which closure was not feasible and either partial or complete coverage with split-skin grafts was required. Such cases are not included in this analysis. The results in these cases on this one ward are fairly typical of the results obtained in some twelve other surgical wards in this hospital.

The wounds are divided into two groups, those in which primary union was obtained and those in which, following secondary closure, some wound complication resulted. The wounds with complications may be subdivided into the following five groups: (1) cellulitis with purulent exudate, (2) cellulitis without purulent exudate, (3) hematomas, (4) severe stitch abscesses, (5) partial or complete wound separation.

We have been rather stringent in our definition of the last group and considered any wounds to fall into this class in which the wound separation measured 1.0 cm. or greater in length. Of the total number of 966 wounds, 96, or 9.9 per cent, fell into the group of wounds with complications.

PROCEDURE

The location of our hospital in relation to the actual zone of combat varied over the eighteen-month period and while the hospital remained stationary, the front moved forward. This gave us an opportunity to observe wounds from within a period of twenty-four hours of their receipt up to twenty to thirty days following débridement. At times we had the unique privilege in military surgery of performing both the débridement and subsequent secondary closure. Accordingly the opportunity presented itself for a broader perspective of the problem than had our experience been limited entirely to that of delayed closures. Our experience has led us to the conclusion that the following routine in the handling of the soft tissue wounds results in the most satisfactory closure and the most rapid restoration of function and subsequent return of the patient to duty.

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Upon the patient's arrival in our hospital, an examination to determine the general condition was carried out, without removal of the dressings unless there was undue pain in the part or an abnormal elevation of pulse and temperature. If an extremity was involved, an effort was made to determine the presence and extent of nerve or blood vessel injury. The dressing was inspected for evidence of hemorrhage and any required roentgenograms were made. If the wounds were anything other than minor, hematocrit and serum protein determinations were made and the patient was typed for transfusion if deemed advisable. Closure was carried out four to six days following débridement if it was at all possible to do so. All elective surgery was made subordinate to the early closure of these wounds. In the operating room, pentothal anesthesia was used in the vast majority of these cases. Following removal of the dressing, the skin surrounding the wound was cleaned with soap and water and ether and irrigated with saline solution. The skin may or may not be painted with an antiseptic. With adequately débrided early wounds of under eight to ten days following débridement little or no granulation tissue has been formed. The skin and subcutaneous tissue overlying the fascia were freed and undermined liberally, if necessary. Frequently, after adequate undermining, wounds which at first appeared impossible of closure come together without undue tension, the skin having retracted and the actual skin loss not being great. Sutures of cotton, silk, or silkworm gut were used with either plain or mattress type sutures, preference being given to plain sutures if the edges did not tend to invert. However, mattress sutures were necessary, in part at least, in the greater number of wounds. In the more severe cases and especially where considerable tension was required, silkworm gut sutures were utilized and we feel that this gave the most satisfactory results in the difficult wounds. Cotton was used in the smaller wounds and the wounds in which there was little or no tension. The sutures were placed closely together at intervals of approximately 1.0 cm. It was frequently felt best, especially in large wounds, to place the sutures before tying them. Postoperative immobilization of the part, we feel, is most important in securing a successful result and plaster casts and posterior splints were used in closures of all wounds of the extremities. We used no sulfónamide drugs locally in any of the wounds. If the patient's hematocrit was below 40, he was given transfusions either before or during the operative procedure. Postoperatively the patient was kept in bed at least until after the first dressing, this being carried out usually on the seventh or eighth day, at which time the greater portion of the sutures were removed. Frequently either alternate or a few central sutures were left in for two or three days longer. The casts, however, were in most instances left off after seven to eight days and early motion was encouraged. Physiotherapy is considered an important aid in early restoration of function. An extremely small number of these patients, unless there was prior evidence of infection, received either sulfonamides or penicillin postoperatively. Small granulating tabs were trimmed with scissors and painted with 10 per cent aqueous solution of mercurochrome. Well-distributed pressure dressings were utilized for the first seven to ten days to obliterate dead space but the pressure was released after the sutures were removed. Drainage was used in thirty-eight cases in this group.

The one prime consideration which we kept constantly in mind in the treatment of these wounds was early mobilization and restoration of function; small granulating areas were not considered an indication for continued immobilization.

RESULTS

Wound Complications.—Of the 966 wounds, 96 resulted in some postoperative complication which may be tabulated as shown in Table I. These wound complications will be discussed and further analyzed later.

Considering together the patients returned to either full or limited duty in the Italian Theater, there were 237 such cases, 75.2 per cent of the total (see Tables II and III).

It is difficult to analyze on a statistical basis the reasons for the postoperative complications. There are, however, certain trends which our analysis reveals and which may be pertinent. We have been interested in determining

TABLE I. POSTOPERATIVE COMPLICATIONS

	WOUNDS	PER CENT
Cellulitis with purulent exudate	18	1.9
Cellulitis without purulent exudate	13	1.3
Hematomas	6	0.6
Severe stitch abscess	4	0.4
Partial or complete separation (any over 1.0 cm.)	55	5.8

TABLE II. HOSPITALIZATION IN ITALY

DAYS	NUMBER OF CASES	PER CENT
Hospitalization of the 315 Patients		
0 to 30	98	31.1
31 to 60	127	40.3
61 to 90	51	16.1
Over 90	39	12.3
Hospitalization for Those Returned to Full Duty (197 Cases)		
0 to 30	71	36.0
31 to 60	94	47.7
61 to 90	18	9.1
Over 90	14	7.1
Hospitalization for Those Returned to Limited Duty (39 Cases)		
0 to 30	0	0.0
31 to 60	13	33.3
61 to 90	16	41.0
Over 90	10	25.6

TABLE III. DISPOSITION OF PATIENTS

DISPOSITION	NUMBER OF CASES	PER CENT
Full duty	197	62.9
Limited duty	39	12.3
To North Africa and other miscellaneous dispositions, ultimate disposition unknown	12	3.8
Zone of interior for soft tissue damage and its complications (nerve and major blood vessel injury excluded) (2 due to thrombophlebitis)	6	1.9
Zone of interior for reasons other than the soft tissue wound	60	19.0

whether or not the time interval, the number of hours elapsing between the occurrence of the wound and the débridement, bore any relation to the success or failure of the subsequent secondary suture. Table IV, of which the facts are demonstrated more graphically in Fig. 1, tends to show that provided an adequate débridement is carried out, the time interval, up to reasonable limits, bears little relation to the success of the subsequent wound closure. This is not indicative that débridement may be delayed with impunity, but merely reveals the relationship in those wounds which were suited to secondary suture. Doubtless delay in débridement in others was responsible for gas-forming infections as well as other types of infections necessitating a much more extensive débridement. These facts are not included and the figures in Table III, therefore, do not give the true over-all picture.

TABLE IV. HOURS TO DÉBRIDEMENT

HOURS	WOUNDS	PRIMARY UNION	PER CENT PRIMARY UNION
1 to 6	158	140	88.6
7 to 12	254	234	92.1
13 to 18	131	122	93.1
19 to 24	140	118	84.2
25 to 36	105	92	87.6
37 to 48	82	79	96.3
49 to 72	79	68	86.0
Over 72	8	8	100.0

Likewise of considerable interest is the relationship of the number of days elapsing between débridement and wound closure to the success of the subsequent closure. This is tabulated in Table V and is likewise shown more graphically in Fig. 2.

TABLE V. DAYS ELAPSING BETWEEN DÉBRIDEMENT AND SECONDARY SUTURE

NUMBER OF DAYS	NUMBER OF WOUNDS	PRIMARY UNION	PER CENT PRIMARY UNION	
3	8	6	75.0	
4	82	80	97.6	459 wounds (95.4 per cent) primary union
5	148	137	92.6	
6	243	236	97.1	
7	73	66	90.4	
8	61	49	80.3	
9	89	77	86.5	
10	84	81	96.4	
11 to 20	144	118	81.9	
Over 20	39	24	61.5	

It is of interest to note that closure in six days or less was highly successful in 459 of the wounds closed, with only twenty-two complications and a resultant 95.4 per cent primary union. As the time interval lengthened, the success of closure became less likely. In addition, the difficulty of the procedure was greatly magnified, the older the wound the more granulation tissue present, requiring excision if the closure is to be successful. Frequently wounds which might have been successfully closed at an early date were of necessity covered with a graft when of long duration.

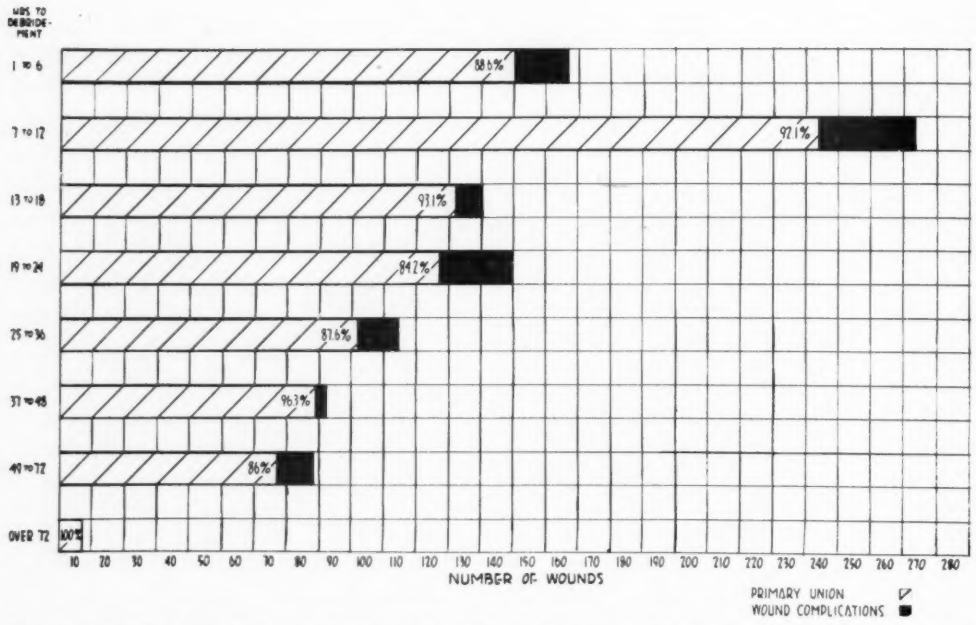

Fig. 1.—Relationship between the number of hours elapsing before wound débridement and the success of the subsequent wound closure.

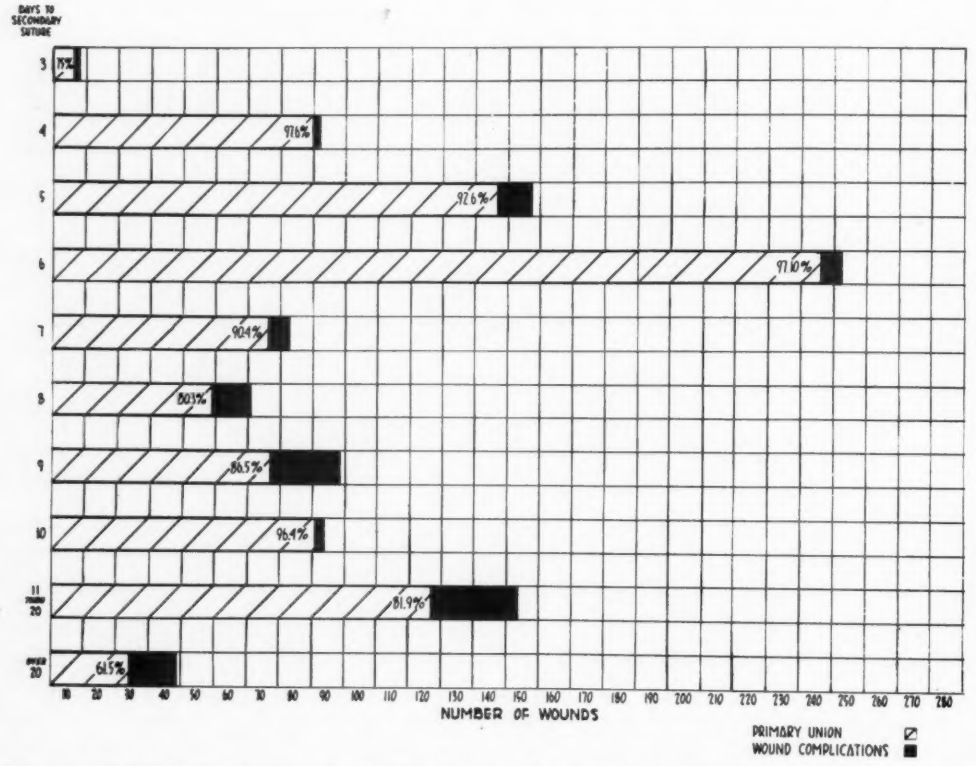

Fig. 2.—Relationship between the number of days elapsing from the time of débridement to secondary suture and the success of the wound closure.

Fortunately, evacuation facilities from the forward installations were excellent. The great majority of patients reached us after a time interval compatible with early secondary suture. The responsibility of carrying out the early closure, therefore, lay primarily on the shoulders of the surgeon in the general hospital.

Another factor, which to a considerable degree is dependent upon the time of closure, but which likewise to some degree is dependent on the judgment of the individual surgeon, is that of whether or not the wound should be excised before closure. In the early wounds, especially those under eight days, previously adequately débrided as mentioned previously, little or no granulation tissue has formed, a considerable portion of the edema has subsided, and the tissues are soft and not fixed. In many of these the skin and subcutaneous tissue can be mobilized and closed. After ten days has elapsed, there is a definite problem due to the firm granulation tissue. The percentage of successful closures of the early wounds which require no excision is high. If the wound is old and excision is of necessity carried out, it is best to perform a total block dissection down to the fascial layer and not temporize with mere trimming of the skin edges and granulation tissue. The results obtained in relation to the necessity of wound excision are tabulated in Table VI and presented graphically in Fig. 3.

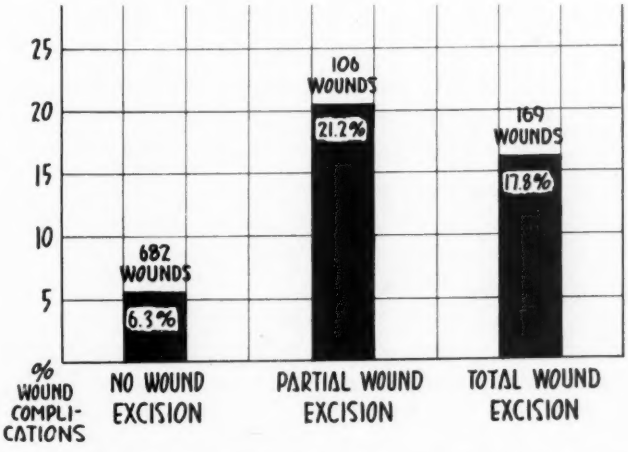

Fig. 3.—Per cent of wound complications in relation to necessity of wound excision.

We used fine silk or cotton, or silkworm gut suture material; cotton being used for the smaller wounds and those which would close without tension while silkworm gut was used in the most difficult closures, in large wounds, and in those in which considerable tension resulted. In some fifty-nine wounds, a layer closure using buried cotton or catgut was used in order to close fascial defects. This has been utilized especially in the popliteal space and on the fascia lata where closure could be carried out without undue tension. In spite of the 27 per cent complications, we feel that in selected wounds it is of considerable value. The high per cent of successful closures using cotton is not indicative of its being a better suture material, but rather that it was being used on the less difficult wounds. It has been our impression that the instance of stitch abscess formation has been greater when using silk sutures.

TABLE VI. PER CENT OF WOUND COMPLICATIONS IN RELATION TO NECESSITY OF WOUND EXCISION

	NUMBER OF WOUNDS	PRIMARY UNION	PER CENT PRIMARY UNION
No excision	682	639	94.7
Partial excision	106	83	78.8
Total	169	139	82.3

TABLE VII. COMPLICATIONS FROM DIFFERENT SUTURE MATERIALS

	WOUNDS	PER CENT OF COMPLICATIONS
Silk	183	10.9
Cotton	434	4.8
Silkworm gut	283	13.7
Layer closure	59	27.0

TABLE VIII. COMPLICATIONS ACCORDING TO SIZE OF WOUNDS

DIAMETER OF WOUND	WOUNDS	COMPLICATIONS	PER CENT OF COMPLICATIONS
Under 2 cm.	209	21	10.4
2 to 8 cm.	660	60	9.1
Over 8 cm.	97	15	15.5

In Table VII are tabulated the number of wounds closed with the respective suture materials and the per cent of complications resulting with each.

The wounds were classified in size according to their greatest diameter and in Table VIII is given the number of wounds in each category with the number and per cent of complications resulting from their closure.

Before closure of the wounds no studies were made to determine the bacterial flora. Clinical judgment alone determined the cleanliness of the wound and its adaptability to secondary suture. Of the total group there were forty-six which were considered dirty wounds. These were treated with either hot wet dressings or excision, or both. In this group twenty-two, or 47.8 per cent, of the patients with dirty wounds had postoperative complications following closure. This emphasized the extreme importance of radical and thorough débridement at the forward installations and the small group of only forty-six wounds is indicative of the excellent débridement done at the evacuation hospitals.

We feel that hot wet dressings should not be used prior to operation on any but the infected wounds. In the first month of work, we treated a few patients with clean wounds with hot wet dressings before surgery and the results were not satisfactory. The leaving of the surgical dressing in situ not only prevents contamination, but the bloody dressings act as an excellent splint. The leaving of the dressing unchanged until the patient is on the operating table assumes that no drains or tight packing have been inserted into the wound at the forward hospitals and in a great majority of cases this was found to have been true.

Of the wounds which did poorly postoperatively, in twenty-six the degree of failure was of such severity that a subsequent procedure was required in

order to secure healing. This was 27 per cent of all the complicated wounds and 2.6 per cent of the entire group. Using the criteria mentioned previously for wound separation, namely, 1.0 cm. in length, there were many in which the degree of failure was mild, this number being fifty-eight, or 60.4 per cent of the complicated wounds. From the viewpoint which is of primary importance, namely, that of prolonging the convalescence, the analysis reveals that there were twenty-nine wounds in which the failure of the original delayed suture was of such degree that the convalescence was prolonged over that which would have occurred had the original closure been successful. These twenty-nine wounds are equal to 3 per cent of the total and therefore we feel that it is this 3 per cent which might be considered poor results and that 97 per cent of the wound closures terminated satisfactorily. There were no deaths in the series.

CONCLUSION

These facts substantiate the supposition that following adequate débridement, early secondary suture of the débrided wound is a highly satisfactory procedure. The facility with which wounds can be closed at this early date has been mentioned. It is important that, barring complications, the original dressing not be disturbed until the patient is on the operating table. The importance of immobilization postoperatively cannot be overemphasized and we feel that bed rest the first week is a definite adjunct. We have used practically no sulfonamides postoperatively although practically all of the patients in the group had previously had sulfonamide crystals dusted into their wounds at forward hospitals and many had received either sulfonamides or penicillin, or both, orally and parenterally. The factor of primary importance which we have kept constantly in mind has been that of early mobilization and restoration of function in order to hasten the return of the patient to useful duty in this theater. No attempt will be made to discuss special problems which pertain to wounds in specific localities, such as the face and hands. Needless to say, these two sites withstand closure under tension very poorly. The suture should be small in caliber and we have removed the sutures in the face and neck in from three to five days and in the hand usually on the fifth day without wound disruption. The most difficult sites of closure were the long shoulder and scapular wounds, so frequently and unfortunately longitudinal in direction, often of considerable length, up to 30 to 40 cm., and frequently with considerable loss of substance. Transverse wounds in this locality close much more readily whereas on the extremities, except in the vicinity of the joints, the longitudinal wound lends itself most readily to closure.

The scars resulting from these closures frequently leave much to be desired. With no fascial closure and often sutured under tension, the scars frequently broaden and some have been seen after six- to twelve-month periods that were quite wide. Although muscle hernias obviously are frequently occurring, we have seen only a rare one which was the cause of pain and dysfunction. Doubtless in the years to come, many of these scars will require excision. For the present, however, the method suffices to secure an early closure of the defect with epithelium, early return of function, and a rapid rehabilitation of the patient.

PLASMA CELL MASTITIS

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DURING the fifteen years since it was first described, plasma cell mastitis has been a subject of increasing interest to surgeons and pathologists. That the disease is one of apparent rarity is attested by the fact that only forty-three cases have been reported in the literature to date. The purpose of this communication is to call this disease to the attention of surgeons again and to report three new cases, two of which present unusual complications.

HISTORICAL REVIEW

The term plasma cell mastitis was first used by Ewing to describe a benign inflammatory disease of the nonlactating breast. The first published report in which this term was used was presented by Cheatle and Cutler[1] in 1931, and was based on cases observed at the Memorial Hospital for Cancer and Allied Diseases, New York, N. Y. Two years later Adair[2] presented detailed reports of the ten cases observed at the same institution up to that time.

Since these preliminary reports,[1, 2, 3] five additional contributions have been made in the American literature. In 1934 C. W. Cutler[4] reported a case showing the typical histological characteristics of plasma cell mastitis, with subsequent development of microscopically similar tumors, probably metastatic, in other parts of the body. This important contribution will be considered in some detail. Subsequent contributions to the literature have been made by Rodman and Ingleby,[5] Miller,[6] Cromar and Dockerty,[7] Payne, Strauss, and Glasser,[8] and Parsons, Henthorne, and Clark.[9]

CLINICAL PICTURE

The importance of plasma cell mastitis lies in the ease with which it may be confused with carcinoma. The disease occurs well within the age limits when carcinoma of the breast may be expected. Adair's patients ranged from 29 to 44 years of age with an average age of 36.3 years, while in the twenty-four cases reported by Cromar and Dockerty, patients averaged 40 years of age. In all published reports the disease has invariably occurred in multiparous women. Elapsed time since the last lactation has averaged four to five years.

Adair has pointed out that the natural history of the disease may be divided into two phases: the acute and the residual. The acute phase consists of a mild inflammatory reaction involving all or a portion of the breast, often associated with increased local heat, redness, and mild tenderness. This phase is transient and the symptoms are usually so mild that the patient does not seek medical advice. After a variable period, ranging from a few weeks to several months, the residual phase, consisting of a nontender tumor, is noted. The tumor at times is accompanied by discharge from the nipple which is

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variously described as "watery or creamy"[2] or "puriform."[6] Nipple discharge was noted in twelve of the thirty-four reported cases in which these data were mentioned.[2, 7] In none of these cases has a bloody nipple discharge been noted, although in Case 1, to be presented here, such a bloody discharge was present for five months preceding operation.

Examination of the involved breast reveals a firm, nontender tumor mass, with an irregular and often ill-defined border. The mass may occupy any portion of the breast but usually partially underlies the areola. The nipple is retracted and the overlying skin is edematous, giving a typical *peau d'orange* appearance such as is seen in malignant lesions. The axillary lymph nodes are usually enlarged. Signs of local inflammation are entirely lacking.

The physical findings in plasma cell mastitis may so closely resemble those of carcinoma of the breast with attachment to the skin and with axillary metastases that many cases have been reported in which radical mastectomy was done without preliminary microscopic study of biopsy material. The diagnosis may be suspected, clinically, by eliciting a satisfactory history of the mild, acute phase of the disease.

ETIOLOGY

Since so little is known of the nature, significance, and function of plasma cells, it is not remarkable that the etiology of plasma cell mastitis is still a matter of conjecture. Ewing, commenting on the original cases reported by Adair, concluded that "while bacterial infection is probably a necessary factor in the process, its influence is less prominent than the chemical effect of decomposing fatty material." Following this line of reasoning, Rodman and Ingleby[5] injected pancreatized milk into the breasts of normal and lactating rabbits as well as into a rabbit in which pseudopregnancy had been induced. A lesion was produced which resembled plasma cell mastitis on microscopic examination. They concluded that ". . . the experiments cannot be held to prove the nature of the substance which is responsible for plasma cell mastitis in the human breast. What they do show, however, is that milk acted upon by enzymes is one way in which the lesion may be produced." The fact that the disease is almost uniformly found in middle-aged, multiparous women who usually give a history of satisfactory lactation suggests that lipids or their breakdown products in some way may be responsible for the unusual cellular reaction. Adair has suggested that improper breast drainage may have an important bearing in this respect.

No satisfactory bacteriologic studies have been reported. Of four cases in Adair's series from which cultures were taken, two showed the presence of unidentified cocci. In two cases material from removed breasts was injected into guinea pigs but the animals did not develop tuberculosis.

Parsons, Henthorne, and Clark[9] observed two cases in which a diffuse comedomastitis coexisted with typical plasma cell mastitis. They speculated that ". . . if comedomastitis exists prior to the extravasation of material from the ducts it may be responsible for the large quantity of material high in lipid content in the inflammatory area." Focal infection in the form of badly diseased tonsils was advanced as a possible contributing cause in another case.

Payne, Strauss, and Glasser[8] have pointed out the similarity of the basic pathology in mastitis obliterans, a disease described by Ingier in 1909, to that of plasma cell mastitis. The proliferation of the subepithelial connective tissue, the obstruction of the ducts by the latter, and the irregular proliferation of the ductal epithelium are, according to them, the most striking characteristics of both diseases. These authors believe that the massive infiltration with plasma cells seen in plasma cell mastitis is nonspecific and merely indicates a chronic inflammatory reaction of long duration.

PATHOLOGY

The gross pathologic lesion of plasma cell mastitis consists of single or multicentric nodules, usually of a yellowish-brown color, occasionally with liquefaction, forming abscesslike cavities. The contents of these cavities, which may be single, multiple, or confluent, vary from puriform material to the color and consistency of butter. The mass varies from soft to firm, often duplicating the consistency of carcinoma. The cut surface reveals thickened and inflamed ducts from which a semipurulent material may be expressed.

On microscopic examination the most striking feature is the massive infiltration of the glandular and interstitial tissues with plasma cells. In some cases these are found in solid sheets, cords, and in round or ovoid masses. More often, however, they are disposed in greatest concentration around the ductal system, and, occasionally, the larger ducts are infiltrated with plasma cells to such an extent that the normal architecture is obliterated.[6] Foreign body giant cells are usually present, sometimes in great numbers, making the differential diagnosis from tuberculosis a matter of concern. These giant cells are often arranged around clear areas which are evidently produced by sheaves of fatty acid crystals which have dissolved during tissue fixation and staining. Eosinophiles in varying numbers are occasionally noted, but other types of leucocytes are usually absent.

A diffuse overgrowth of periductal connective tissue often causes partial obliteration of duct lumens and, by extending into the supporting tissue, accounts for the retraction of skin and nipple which is so commonly noted clinically. Dilated ducts are often filled with cellular debris desquamated from the lining epithelium.

The marked hyperplasia of the epithelium lining the ducts has been commented upon by almost all authors, the cells frequently being piled up eight or ten rows high.[10] That this epithelial hyperplasia presents serious potentialities of malignancy is evident from Case 2, presented here, in which a typical comedocarcinoma coexisted with massive plasma cell infiltration.

Plasma cell mastitis may be indistinguishable from plasma cell tumor of the breast. After a thorough review of the reported cases of extramedullary plasmacytomas, Hellwig[11] concluded that "The plasma cell tumor may arise in almost any situation in the body and may behave clinically as a simple benign growth or as a neoplasm of the most malignant type. From the prognostic standpoint, the localization and the gross appearance seem to be more reliable criteria than the histologic structure." The case reported by C. W. Cutler[4]

demonstrates that such tumors may arise in breast tissue. This patient was a 49-year-old woman from whose left breast a tumor was removed by local excision. Because the microscopic appearance seemed characteristic of plasma cell mastitis, further surgery was abandoned on the basis of a benign lesion. Nine months later a growth with apparently identical microscopic characteristics was found on the right vocal cord, and metastases later occurred in the left sternoclavicular joint, the upper portion of the left breast, and the right antrum.

CASE REPORTS

CASE 1 (Framingham Union Hospital No. 57,913).—A 45-year-old white woman, the mother of four children, was admitted to the hospital March 9, 1943. One year previously, following an upper respiratory infection, slight tenderness and heaviness of the left breast was noted. This disappeared spontaneously in about one week. Thereafter she remained well until five months before admission when a slight, bloody discharge was noted from the left nipple. This was intermittent, lasting one day at a time and usually most evident about one week before the onset of the menstrual periods. During the two weeks preceding admission the sanguineous discharge was continuous and, during the last three days, somewhat purulent. A tumor was first noted in the left breast by her physician two weeks before admission. The menstrual periods were regular with no recent change in the type or quantity of flow. There had been no recent change in weight and there was no family history of neoplastic disease.

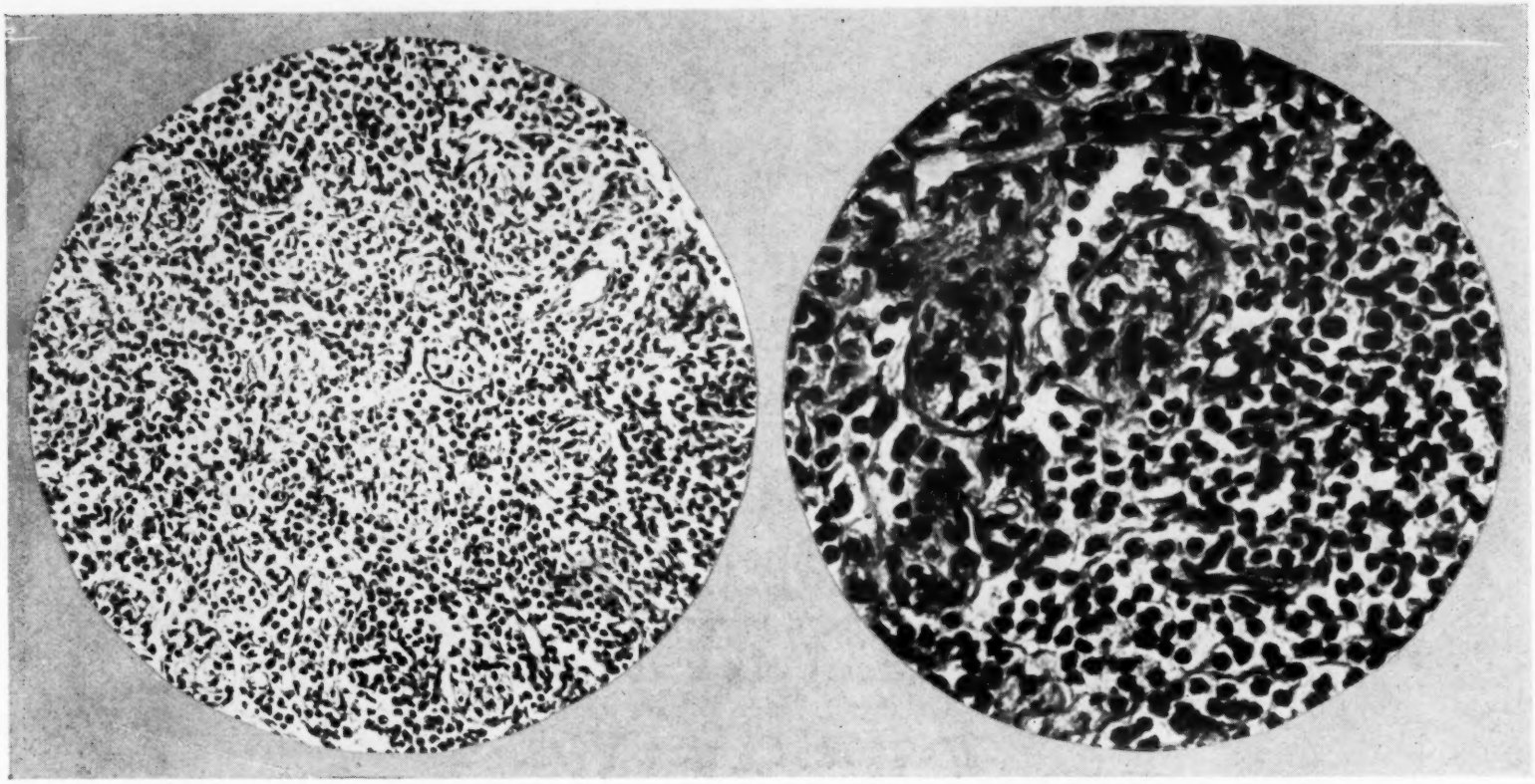
The general physical examination revealed no abnormalities. The right breast was normal in all respects. In the upper, medial quadrant of the left breast was an irregular, nontender tumor 2.5 cm. in diameter. The overlying skin showed a typical *peau d'orange* appearance but there was no attachment to the underlying muscles. Pressure over the tumor caused the discharge of a drop of serosanguineous fluid from one of the nipple openings. Both nipples were slightly inverted but there was, in addition, definite retraction of the left nipple.

Laboratory studies showed the urine to be normal. There was a mild hypochromic anemia with red cell count of 3,790,000 and hemoglobin of 71 per cent. The white cell count was 13,300 with 69 per cent segmented forms, 28 per cent lymphocytes, 2 per cent basophiles, and 1 per cent eosinophiles. Blood Wassermann and Hinton tests were negative. X-ray examination of the chest showed no abnormality.

A preoperative diagnosis of intraductal papilloma or papillary carcinoma was made. At operation the mass, overlying skin, nipple, and areola were excised and submitted to the pathologist for immediate section and microscopic study. Following the report of plasma cell mastitis the biopsy wound was closed, the skin reprepared, and a simple mastectomy done through a modied Greenough incision.

Section of the removed mass showed it to consist of two small cavities which were filled with thick, gray-brown, purulent material. The cavities were surrounded by an area 4.4 cm. in diameter, orange yellow in color, and rather soft. The remainder of the breast showed no gross abnormalities.

Microscopic examination (Fig. 1) showed the tissues surrounding the cavities to be densely infiltrated with plasma cells. Occasional foreign body giant cells and rare eosinophiles were noted. In the peripheral portions of the mass the plasma cell infiltration was less dense and was chiefly confined to the periductal regions. The ducts showed a considerable variation in size with a tendency to retention of secretion and dilatation. The epithelial lining was markedly hyperplastic, in some areas completely filling the lumens. The epithelial cells displayed wide variations in size and shape but no mitotic figures or other evidence of malignant change were noted. There was a moderate increase in periductal fibrous tissue. Sections made from outlying portions of the breast showed less epithelial hyperplasia than was noted within the confines of the tumor, while the periductal plasma cell infiltration was slight or totally absent.



A. *B.*

Fig. 1. (Case 1).—*A*, Low power and, *B*, high power views showing massive plasma cell infiltration and hyperplasia of duct epithelium.

The postoperative convalescence was uneventful. When last seen, thirty-two months after operation, there was no evidence of recurrence in the scar and no masses were palpable in the opposite breast.

CASE 2 (Massachusetts Memorial Hospitals No. 297,399).—A 76-year-old Negro woman was admitted to the hospital on July 20, 1943, complaining of a tumor in the left breast of two months' duration. There was no history of trauma to the breast, and no local pain or tenderness. The menopause had occurred thirty years previously. She was the mother of ten children, only two of whom were living.

Physical examination showed her to be remarkably well preserved for her years. Except for slight cardiac enlargement with a blowing systolic murmur at the apex and a blood pressure of 240 systolic, and 102 diastolic, the general physical examination showed nothing of note. The right breast was normal. In the upper outer quadrant of the left breast was a firm, nontender, irregular mass 2.5 cm. in diameter. This mass was not attached to the overlying skin or to the underlying structures. A few small, discrete nodes were felt deep in the left axilla.

Laboratory studies revealed the presence of diabetes mellitus, with a fasting blood sugar of 340 mg. per cent. Red blood cells and hemoglobin were within normal limits. The leucocyte count was 10,000 with 68 per cent segmented forms. X-ray examination of the chest showed no evidence of metastatic disease. The electrocardiogram showed left axis deviation.

Following control of the diabetes, operation was performed July 28, 1943. The mass was biopsied and immediate microscopic examination of frozen section material showed evidence of malignant disease. A radical mastectomy was done, from which the patient made an uneventful recovery. When last examined, Nov. 16, 1945, no evidence of residual malignancy was found.

Section through the tumor revealed it to be lobulated, moderately soft and friable, and to vary from yellow to dark crimson. The regional lymph nodes were firm, enlarged, and, on section, presented a homogenous, moist, grayish-pink surface.

Microscopic study (Fig. 2) of sections through different portions of the breast showed a somewhat varied picture. The most striking features were a dense and widespread infiltration with plasma cells associated with an abundant overgrowth of intraductal epithelium which was obviously neoplastic in character. The plasma cell infiltration was most marked in the periductal regions where small numbers of eosinophiles and lymphocytes were also noted. The epithelial cells showed great variation in cytologic structure, low cuboidal, vesicular, pale-staining cells prevailing. Frequent atypical mitotic figures were noted. Cells with an identical appearance were seen breaking through the walls of the ducts and infiltrating the surrounding tissue. These infiltrating cells were arranged in thin cords or in irregularly shaped alveoli and were surrounded by, or intimately mixed with, the heavy plasma cell infiltration. No evidence of neoplastic change was noted in the plasma cells per se.

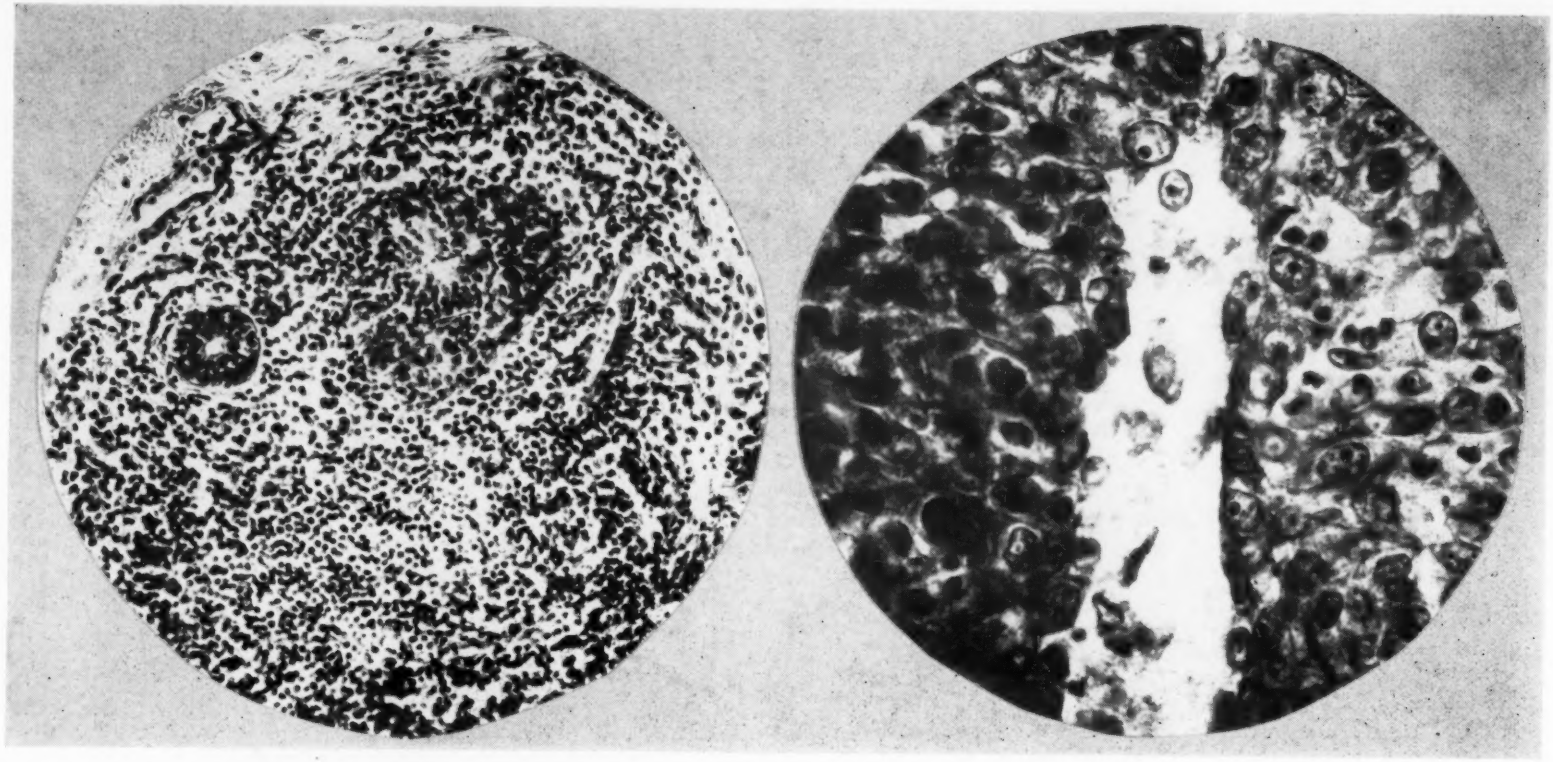
Some of the axillary lymph nodes were more or less completely replaced by broad, irregular, medullary cords of epithelial cells similar to those observed in the primary neoplasm. Many atypical mitoses were present and there was no attempt at gland formation. Surrounding the epithelial cells were large masses of plasma cells.

CASE 3 (Newton Hospital No. H—4434*).—A 55-year-old white married woman was admitted to the hospital June 5, 1942, complaining of a mass in the left breast of two months' duration. Hysterectomy and bilateral salpingo-oophorectomy had been done twenty-five years previously. Otherwise past history was noncontributory.

When first noted the mass was about 1.3 cm. in diameter but the patient believed there had been subsequent slight enlargement. There had been no nipple discharge and there was no history of local pain or tenderness.

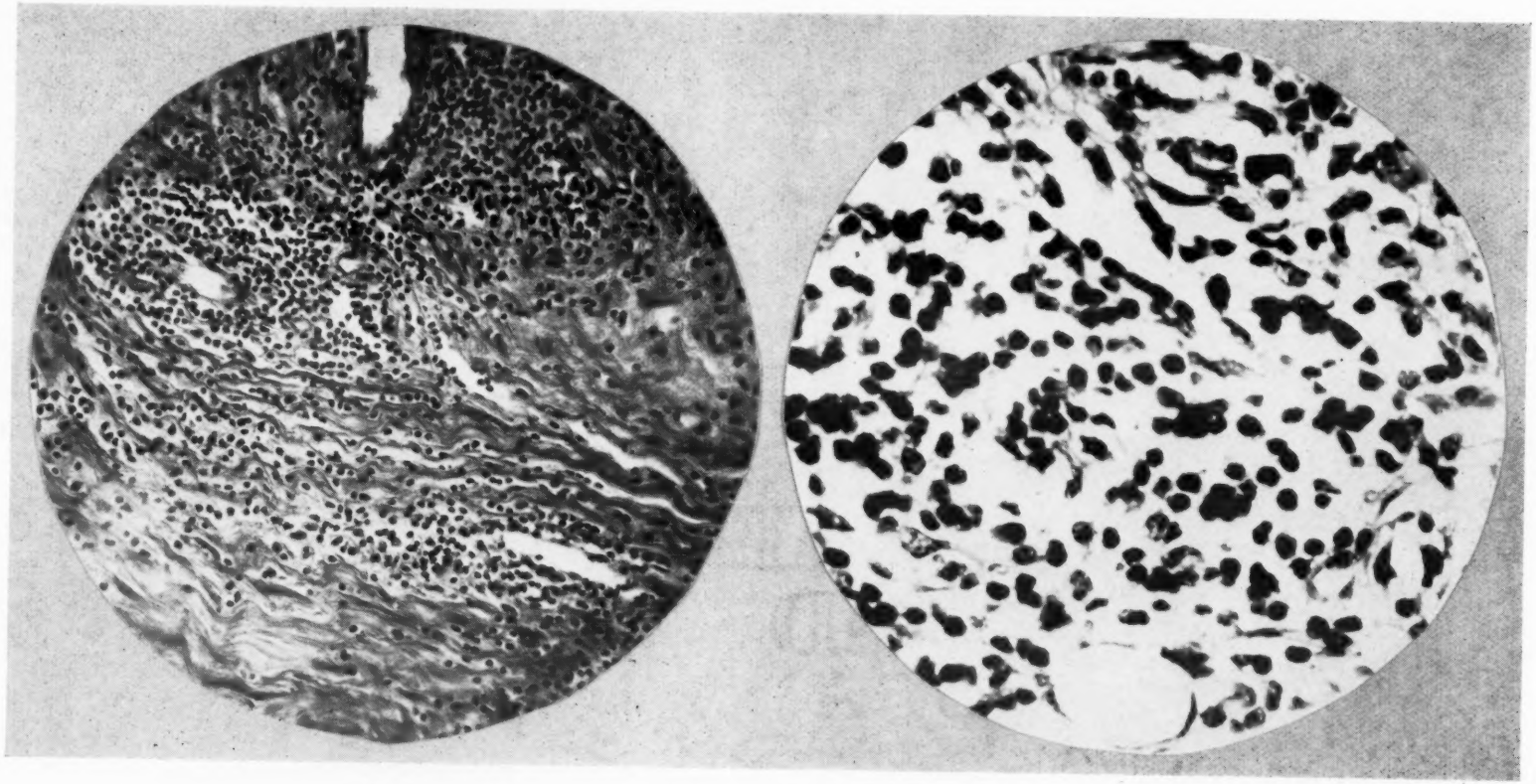
Physical examination showed no significant abnormalities except in the left breast where there was an easily palpable mass 2.0 cm. in diameter. The skin overlying the mass had a

*Dr. E. D. Leonard kindly permitted study and publication of this case.



A. *B.*

Fig. 2 (Case 2).—*A*, Low power view showing massive plasma cell infiltration surrounding ducts, one of which shows malignant change. *B*, Intraductal epithelium showing closely packed, malignant cells.



A. *B.*

Fig. 3 (Case 3).—*A*, Low power view showing increased fibrous tissue stroma, diffuse plasma cell infiltration with periductal concentration and paucity of ducts; *B*, high power.

typical *peau d'orange* appearance but there was no retraction of the nipple. No nodes were palpable in the axilla and laboratory studies showed no significant deviation from the normal.

At operation the tumor and overlying skin were excised with a wide margin. Microscopic examination of frozen section material was mistakenly interpreted as showing evidence of malignancy and radical mastectomy was performed. The postoperative recovery was uneventful and the patient has remained well.

Section of the removed tumor showed it to consist of a stony hard, white mass 2 cm. in diameter with no evidence of encapsulation or central softening. Serial section of the remainder of the breast showed nothing of note. Seven lymph nodes were found in the axillary fat, ranging from 0.5 to 1.0 cm. in diameter.

Microscopic examination of the tumor (Fig. 3) showed an increase of fibrous tissue stroma, diffusely infiltrated with plasma cells, but with a notable periductal concentration. At scattered points foreign body giant cells were seen singly or in small groups. A few clear areas, probably produced by dissolved sheaves of fatty acid crystals, were surrounded by giant cells. The ducts, which were small and relatively few in number, showed definite hyperplasia of the lining epithelium. No abnormal proliferation, invasion, or other evidence of malignancy was noted. Appropriately stained sections showed no tubercle bacilli. The axillary nodes showed no histopathology.

DISCUSSION

The uniformity of the clinical and microscopic findings in typical plasma cell mastitis, such as in Cases 1 and 3 reported here, is striking. At the same time doubt has been expressed as to whether the plasma cell reaction is a primary and essential part of a clinical and pathologic disease entity.[8]

From the clinical standpoint it would seem that such symptoms as tumor, nipple discharge, and skin and nipple retraction could be satisfactorily explained on the basis of epithelial hyperplasia and periductal fibrosis. Perhaps the only part of the clinical picture which might be attributed to the plasma cell reaction is the early acute phase described by Adair.

From the histologic standpoint it is well known that plasma cells are found in a great variety of disease processes in which they are considered important only as indicating the presence of an inflammatory process of long duration. Therefore, if the plasma cell reaction is merely incidental to some other pathologic process, the advisability of the term plasma cell mastitis, which places stress on this secondary manifestation, has been questioned. To overcome this nomenclatural disadvantage the suggestion has been made[12] that plasma cell reaction be used as a suffix to point out this unusual tissue response, at the same time naming the pathologic condition which may have elicited it. Thus, Cases 1 and 3 might be termed "glandular cystic hyperplasia with plasma cell reaction" or "chronic mastitis with plasma cell reaction," while Case 2 could properly be termed "comedocarcinoma with plasma cell reaction."

In Case 1 there was a sanguineous nipple discharge. In view of the marked hyperplasia of the epithelium lining the ducts, it seems probable that this symptom will be encountered in a small percentage of cases.

Case 2 is of particular importance because it illustrates the concomitant development of comedocarcinoma in a breast which was the site of a plasma cell reaction. While this is the first case that has come to our attention in which the two conditions have coexisted, the epithelial hyperplasia noted by all authors suggests that such a combination is more than coincidence. This case, together with that reported by C. W. Cutler in which the disease, or one

microscopically identical with it, metastasized as a plasmacytoma, suggests that plasma cell mastitis, while usually a benign disease, has definite malignant potentialities which may develop in either, or possibly both, of two directions: (1) As a malignant epithelial neoplasm of the comedocarcinoma type, probably the result of dedifferentiation of the hyperplastic ductal epithelium or (2) as a malignant plasmacytoma. In addition, Parsons, Henthorne, and Clark observed two cases in which local recurrence, without distant metastases, followed simple excision of the tumor mass.

These considerations would seem to clarify the problem of treatment. Biopsy and immediate microscopic examination of frozen section material should be carried out in all breast tumors, including those in which the clinical findings are characteristic of malignancy. When the diagnosis of plasma cell mastitis is established histologically, simple mastectomy would seem to be the operation of choice, at least until more is known of the etiology and natural history of the disease. Sections from many parts of the removed breast should then be carefully studied for evidence of malignancy. If such evidence is found, subsequent removal of the pectoral muscles and radical axillary dissection are, of course, indicated. Even though histologic evidence of malignancy is not found, careful follow-up examinations for evidence of local or distant recurrence should be made for several years following operation.

SUMMARY

1. The etiology and pathology of plasma cell mastitis are reviewed.

2. Three new cases of plasma cell mastitis are reported. One of these patients had a sanguineous nipple discharge for five months preceding operation. In another there was a coexistant comedocarcinoma which had metastasized to the axillary nodes.

3. The relationship of plasma cell mastitis to malignancy is discussed.

4. The treatment of choice consists of simple mastectomy, followed by careful histologic study for evidence of malignancy.

5. The importance of adequate follow-up study is stressed.

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SECONDARY DAMAGE IN WOUNDING DUE TO PRESSURE CHANGES ACCOMPANYING THE PASSAGE OF HIGH VELOCITY MISSILES

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INTRODUCTION

BY PRIMARY damage in wounding we refer to injury directly traceable to changes accompanying the movement of the missile. When a high-velocity bullet enters the body and ploughs through tissue, it is obvious that material in its path will be thoroughly disintegrated. A *permanent cavity*, filled with blood and pulped cells, is gouged out. In addition, immediately behind the moving missile, a large *temporary cavity* appears, many times the cross-sectional area of the missile itself. This temporary cavity quickly subsides, but tissue at its periphery has been greatly stretched and cells may be injured. Small blood vessels and capillaries are ruptured. There is left a considerable *region of extravasated blood* around the missile track. Changes in these three regions —the temporary cavity, the permanent cavity, and the region of extravasated blood—result in primary damage, which might be used as a direct measure of wounding. Photographs illustrating these phenomena will be found in a previous paper[1] which contains references to the literature.

We propose in this communication to consider what may be called secondary damage in wounding, which is the result of pressure changes accompanying the passage of a bullet. Reference has already been made (Puckett and associates[2]) to such effects in the abdomen where perforation of the intestines was found to be connected with rapid expansion of gas pockets, which stretched and tore the tissues, acting like secondary cavities. Secondary damage in wounding is quite comparable to injury from underwater blast where pressure changes cause damage to men and animals in the water. This damage also occurs only at air pockets in the body, resulting in intestinal perforations or lung hemorrhage (see Williams,[3] McMullin and co-workers,[4] Corey,[5] Friedell and Ecklund,[6] Clark and Ward,[7] and Clark[8]).

MEASUREMENT OF PRESSURE CHANGE

The pressures dealt with in this study have come from 1/8 or 3/16 inch steel spheres, weighing 130 and 440 mg., respectively, which have struck the liquid or tissue with velocities varying between 2,800 and 4,800 feet per second. The magnitude of the pressure change is great and the duration must be measured in microseconds or milliseconds. Nevertheless, several methods of measurement are available.

An exact method, which follows rapid time changes in temperature, measured in microseconds, makes use of a piezoelectric crystal tourmaline. When

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subjected to hydrostatic pressure, tourmaline develops a charge the voltage of which can be amplified and recorded with a cathode ray oscillograph. Such records have recently been made in the Princeton biology laboratories when a high velocity steel sphere is shot into a tank of water or passes through the abdomen of an anesthetized cat (Harvey and associates[11]).

Other types of pressure gauge are too slow to follow faithfully the rapid pressure changes but will indicate the direction of pressure change. A simple and instructive method is the use of small masses of gas as pressure indicators. For this purpose rubber balloons about ½ inch in diameter are suspended by threads attached to the bottom of a tank of water with plexiglass sides. Steel spheres are shot into the water among the balloons and a high-speed moving picture of the changes is taken. Contraction of the balloons indicates increased pressure, and expansion decreased pressure. Four disadvantages may be noted: (1) the balloons may not instantly respond to pressure changes; (2) once the balloons have been compressed by a pressure increase they expand and pulsate with their own period superposed on slower pressure changes in the tank itself; (3) shape changes also accompany volume changes of the balloons, so that increase or decrease in volume cannot be determined accurately; (4) introduction of the balloons so changes the system that pressure distribution in absence of balloons cannot be recorded accurately. These four disadvantages combine to prevent an accurate measure of pressure changes from balloon size and Boyle's law, but the trend in pressure is definitely apparent. Their great advantage lies in the fact that pressure changes in many different locations can be visualized simultaneously. The balloons also imitate very closely the behavior of gas pockets in the animal.

THE SIMILARITY OF A SHOT INTO WATER OR FLESH AND AN UNDERWATER EXPLOSION

Practically all observers of wounding by high-velocity missiles have compared their effects to an explosion in the body because of great damage to tissues at some distance from the bullet path. In any underwater explosion there is formed a large cavity or "bubble" quite comparable to the temporary cavity left by a high velocity missile. The cavity behind a shot is shown in Fig. 1 and the explosion in Fig. 2. After attaining a maximum size, these cavities contract and then pulsate at a rate which is dependent on their maximum volume. The maximum volume in one case (the shot) is proportional to the kinetic energy of the striking missile, in the other case (the explosion) to the heat of detonation. It is therefore possible, knowing the striking energy of a missile, to calculate not only the size of the temporary cavity it will produce, but also to state that the effect will be the equivalent of a definite number of milligrams of TNT exploded in the body.

In both cases very similar pressure changes occur around the cavity. We shall first compare the pressure changes in an underwater explosion with those which accompany a shot into water in a tank and then apply these to conditions in the body. The use of water is justified since the soft tissues behave like a liquid system. The pressure changes are of three kinds: (1) shock wave pres-

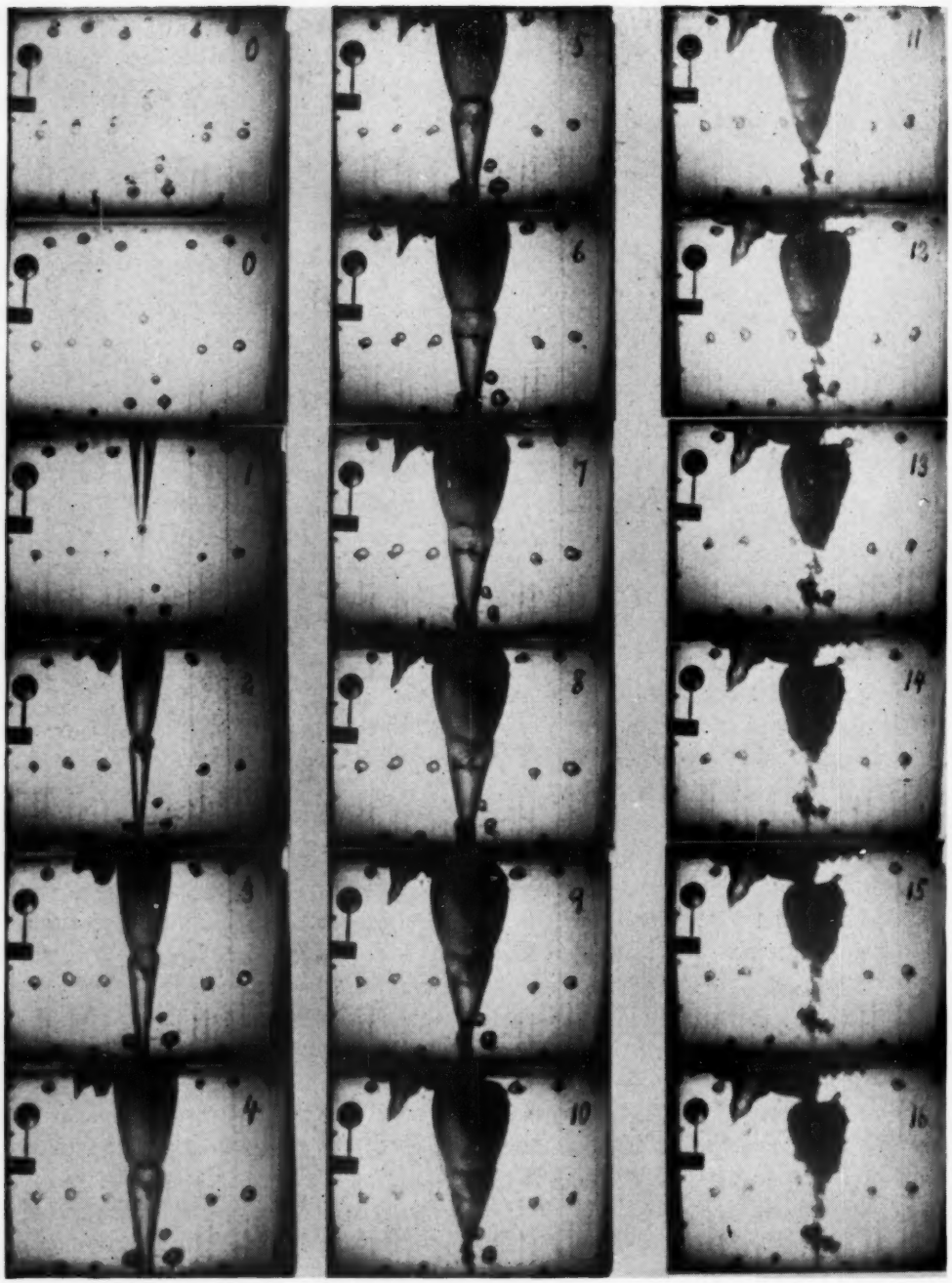

Fig. 1.—Motion picture (166) frames (2,160 per second) of a ⅛ inch steel sphere (impact velocity 3,000 feet per second) striking the surface of water (indicated by arrow) in which are suspended small rubber balloons. The development of the temporary cavity is well shown. Pressure changes in the water are indicated by contraction and expansion of the balloons. Successive frames are numbered. The vertical dots on the left are 5 cm. apart.

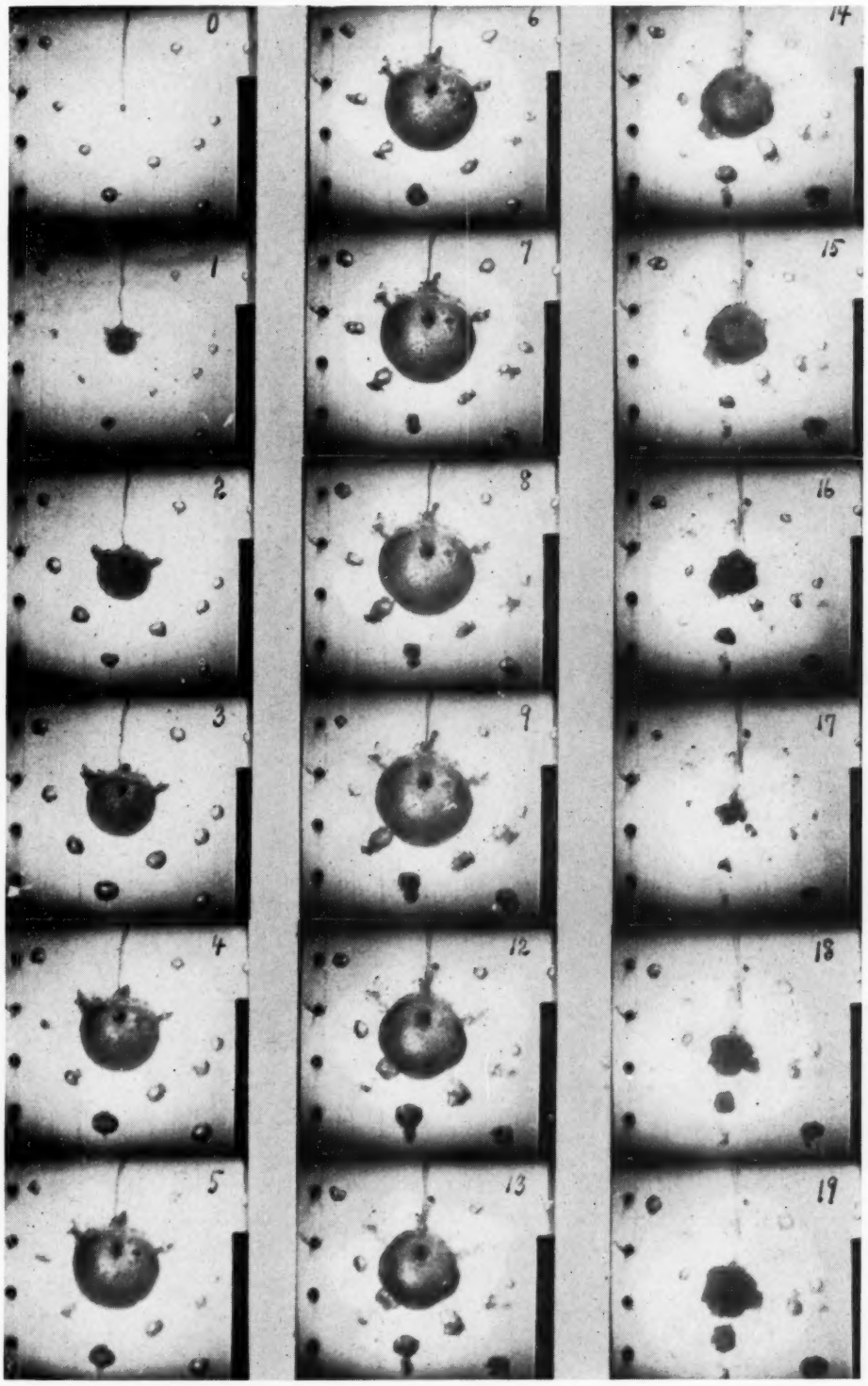

Fig. 2.—Motion picture (25 E) frames (about 2,160 per second) of the detonation of a cap containing 30 mg. of explosive. The expansion and first contraction (Frame *17*) of the explosion bubble are well shown. Small rubber balloons have been suspended in the water to detect pressure changes. The vertical row of dots on left are 5 cm. apart.

sures or sharp, high-pressure pulses, formed when the missile hits the surface of the water or when the detonation occurs; (2) very high-pressure regions in front of the moving missile or around the early detonation bubble; (3) relatively slow, low-pressure changes accompanying the expansion and contraction of the temporary cavity formed behind the missile or around the expanded bubble of gas from the explosion of the underwater charge. Considerable space must be devoted to these pressure changes in simple liquid systems in order to understand what happens in tissues.

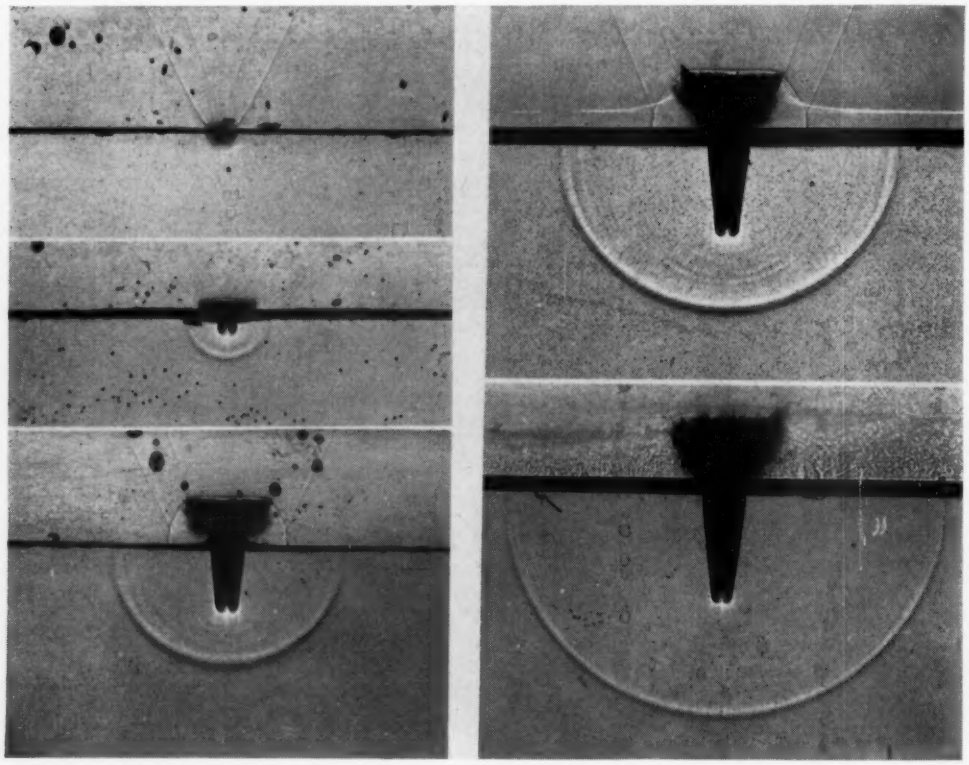

Fig. 3.—A series of spark shadowgrams (S68, S31, S71, S90, S21) of ⅛ inch steel spheres taken at successively longer time intervals after the sphere has hit the water surface. Note how the shock wave, moving 4,800 feet per second, leaves the retarded sphere behind. The striking velocity in all shadowgrams is 3,000 feet per second except the second where it is 1,772 feet per second.

SHOCK WAVES IN LIQUIDS

An exhaustive study of shock waves formed by small high-velocity missiles striking water has been made in this laboratory by McMillen[9] and McMillen and Harvey.[10] These sharp high-pressure pulses move away from their point of origin with the velocity of sound, 4,800 feet per second.* The shock wave front pressure rises instantly to a high peak value and falls off more slowly behind. The peak pressure varies directly as the projected cross-sectional area of the missile and as the square of its impact velocity, but inversely as the

*A shock wave in water moves slightly more rapidly than a sound wave, but the increase is not great, about 5.5 per cent for a shock wave of 14,500 pounds per inch^2 peak pressure.

distance from point of origin. At the water surface the shock wave pressure becomes enormous and equals the pressure on the face of the striking sphere. Energy for shock wave formation thus comes from the kinetic energy of the missile. It is obvious that tissue struck by such high-pressure pulses might be damaged. The evidence for and against such damage will be considered shortly.

Shock waves from underwater explosions are similar to those from missiles hitting water. Waves from large detonations may be measured in tons per inch^2 and are known to injure or to kill men at a considerable distance in the water. The energy for their formation comes from the heat of explosion, about one-third to one-half of which goes to form the shock wave, the remainder going into the expansion of the gas bubble.

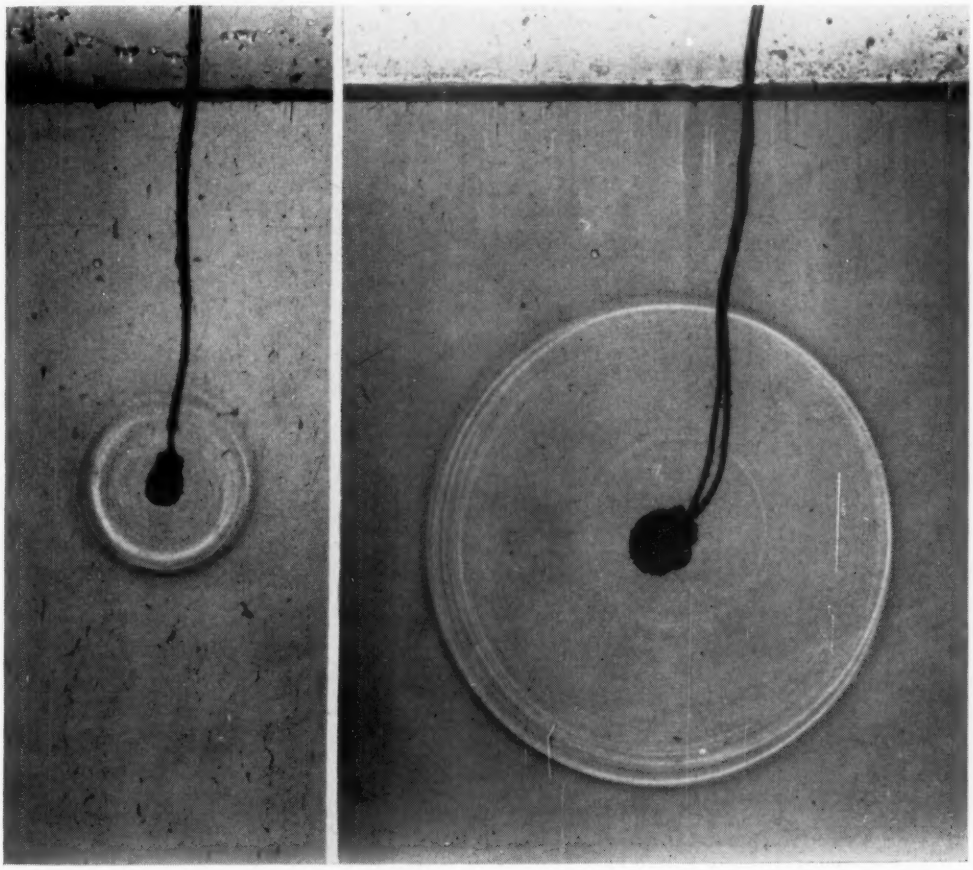

Fig. 4.—Spark shadowgrams of the shock waves from a detonator cap containing 30 mg. of explosive.

Because of the high pressures in a shock wave, the water is compressed and the refractive index changes. This change is shown clearly in a spark shadowgram. In Fig. 3 is reproduced a series of shock waves moving away from a steel sphere striking the surface of the water, and in Fig. 4 shock waves from an underwater explosion. In both cases the spherical wave appears as an advancing

absence-of-light band (dark in a print) changing to a light band behind the wave front. The small secondary waves are due to vibration of the steel sphere. Similar waves move through tissue when struck by high-velocity missiles.

MOVING SPHERE PRESSURE

The pressure immediately in front of a moving sphere is enormous, measured in thousands of atmospheres. It is numerically equal to $\frac{1}{2} \rho V^2 C_D$, where ρ is density of the medium, V velocity of the missile, and C_D the drag coefficient, which, for spheres in water, has the value 0.298. This moving sphere pressure is visualized in Fig. 5, a spark photograph of a steel sphere moving in water behind a grid of lines on a plexiglass plate. The distortion of the lines in front and also at the sides of the sphere is due to a change of refractive index resulting from compression of the water. The moving sphere has its analogy in an underwater explosion, where it is represented by the enormous pressures of the hot gases formed during the detonation.

The moving sphere pressure falls off in front of the sphere to values above an atmosphere; then the pressure rises again, to culminate in the shock wave peak. Since the shock wave is spherical around an explosion, the pressure distribution is radially symmetrical with the detonation point as a center, whereas the missile starts a hemispherical wave from the water surface and pressure gradients are axially symmetrical around the bullet path; a high pressure always exists in front and at right angles to the missile as it advances.

PRESSURES AROUND THE EXPLOSIVE OR TEMPORARY CAVITY

When the shock wave has moved well away from its point of origin and the temporary cavity or explosion bubble is still expanding, the pressure distribution becomes greatly changed. Subatmospheric pressures follow the previously described increased pressures and extend over wide regions around the cavity. They change as the temporary cavity or bubble pulsates, increased pressure accompanying expansion and decreased pressure accompanying contraction. Since these relatively slow, relatively small pressure changes are of great importance in wounding, they have been measured accurately and will be considered in detail.

Making use of small air-filled balloons as pressure indicators, a general idea of the pressure changes in a tank of water can be obtained from Figs. 1 and 2 which are prints from individual frames of a high-speed moving picture (about 2,000 frames per second). In Fig. 1 the balloons reveal the pressure distribution during a high-velocity shot into water and in Fig. 2 after a detonation under water.

In both figures the zero frame shows the size of balloons before the shot. In Frame *1*, balloons near the initially expanding cavity are small, indicating high pressure due to the shock wave. In Frame *2* balloons near the still expanding cavity are large, while those away from the cavity are small. The pressure region has moved out as the cavity expands and is followed by a region of subatmospheric pressure around the cavity. This subatmospheric region increases in size, and in Frame *3* practically all the balloons in the tank are

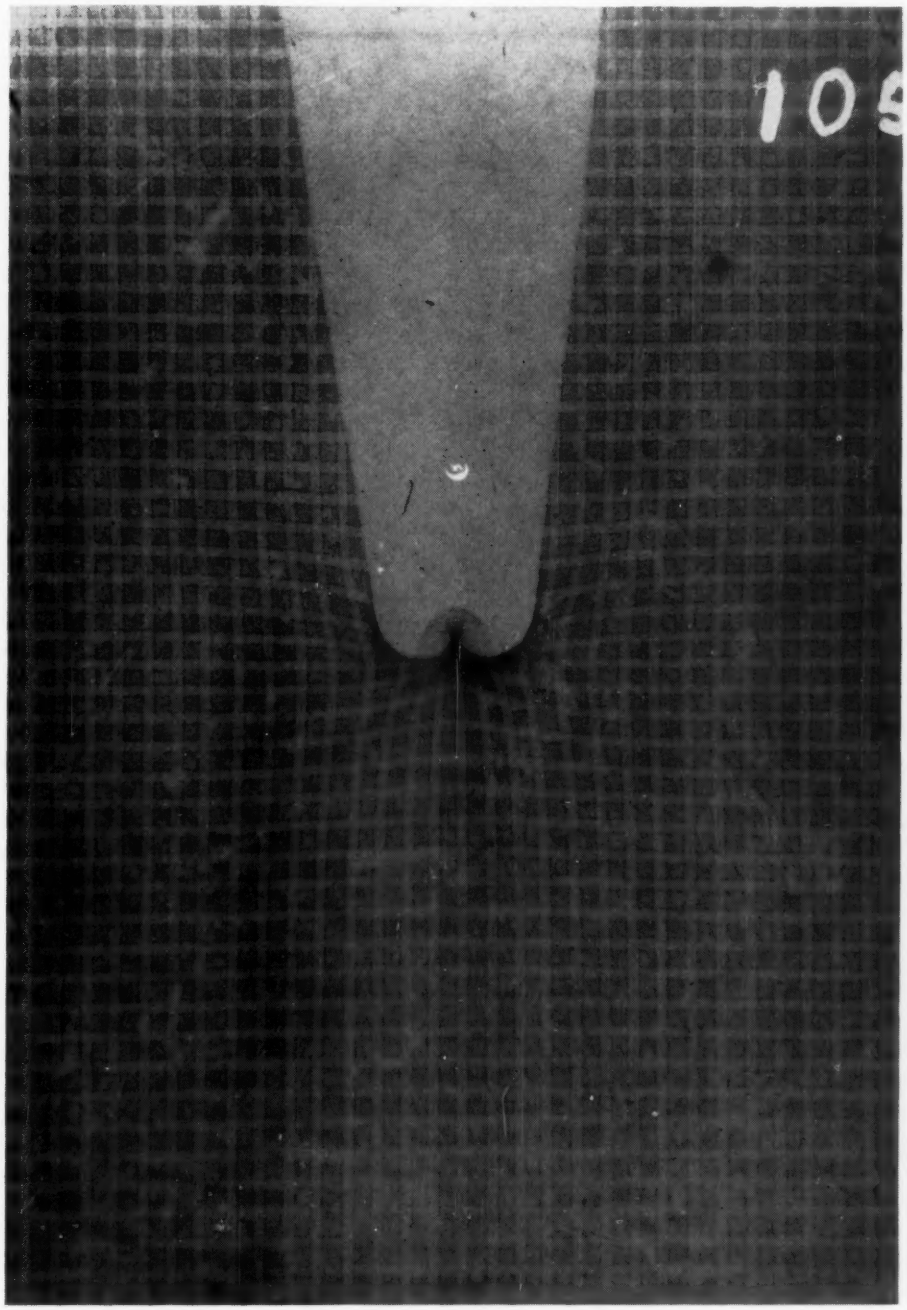

Fig. 5.—An enlargement of a spark shadowgram (D105) of the region around a 9/32 inch steel sphere (impact velocity 3,000 feet per second which has penetrated 5 cm. of water. The high pressure near the missile is revealed by the distortion of a 1 mm. grid placed between spark and sphere.

much larger than in Frame *0*. In later frames the balloons undergo shape changes and volume oscillations while the cavity (or bubble) is still increasing in volume. These minor oscillations are believed to indicate the natural period of the balloons, about 0.002 second.

There appears to be a relatively long period of subatmospheric pressure following the initial sharp pressure increase of the shock wave and while the cavity is still expanding. This decreased pressure is due in part to overexpansion of the cavity (or bubble) and in part to Bernoulli lowering of pressure as a result of the high radial velocity of water around the expanding cavity.

A very considerable difference exists in the initial pressure within the cavity behind a bullet and within the bubble of an underwater explosion. In the former the pressure is always subatmospheric from the start. The missile pushes the water aside as it moves forward, compressing and imparting momentum to the liquid, thereby leaving a partial vacuum, because not enough air flows in to maintain atmospheric pressure. In an explosion cavity or bubble, made up of the gaseous products of explosion, the pressure is at first positive and very high. It is this gas under pressure formed in a few microseconds that suddenly compresses the water, starting the shock wave and giving the water its momentum.

In either case, once momentum has been imparted to the water, its inertia leads to an overexpansion of the cavity, with the development of subatmospheric pressures in the liquid. When this inertia is overcome by the tank walls and pressure of the atmosphere, the cavity volume decreases, resulting in contraction to a minimum volume and a second development of pressure. The air in the cavity is compressed. Following this there is a second expansion. The cavity then pulsates at a rate which can be calculated from the energy delivered to the water. Alternate increase and decrease of pressure accompany the pulsations.

The second pressure development can be seen clearly in Frame *17*, Fig. 2. All the balloons around the contracted mass of explosive gases are greatly contracted. The second pressure development during the cavity minimum in the shot into water (Frame *16*, Fig. 1) is not so marked but can be recognized. The amplitude of pulsations of the temporary cavity are also not as great.

The pressure changes during cavity pulsation are best seen in a pressure record. Such a tourmaline crystal record, of the first three pulsations after a shot ($\frac{3}{16}$ inch sphere moving 3,000 feet per second) into a tank of water, is shown in Fig. 6. The time scale is in milliseconds and the shock wave peak is a thin vertical line that extends off the record. The small rapid pressure changes with a frequency of about 3,000 per second, superposed on the first part of the record, probably come from the vibration of the tank walls. It was possible to produce similar vibratory pressure changes by striking the tank with a hammer.

In Fig. 7 are reproduced frames from a motion picture of the events in the tank, taken at the same time as the tourmaline crystal pressure record. By comparison of picture frames and crystal record it is possible to correlate movement and pressure. It will be observed that when the temporary cavity volume is at a minimum the pressure is approximately a maximum. The first peak

comes 11 milliseconds after the shock wave and represents a pressure of about 60 pounds per inch^2; the second peak is 10 milliseconds later, 21 pounds per inch^2; the third 9 milliseconds after the second, about 7 pounds per inch.^{2}

Subatmospheric pressures between the peaks are particularly marked. The first two, about 15 pounds per inch^2 below the atmosphere, may even indicate a slight negative pressure, that is, a pressure below zero or a tension.

It should be particularly noted that the record shows no pressure changes which occur with the same frequencies as the small oscillations of the balloons of Fig. 1. This fact indicates that these balloons must be oscillating with their own natural frequency, about 500 per second, which is superimposed on the larger volume changes connected with cavity behavior.

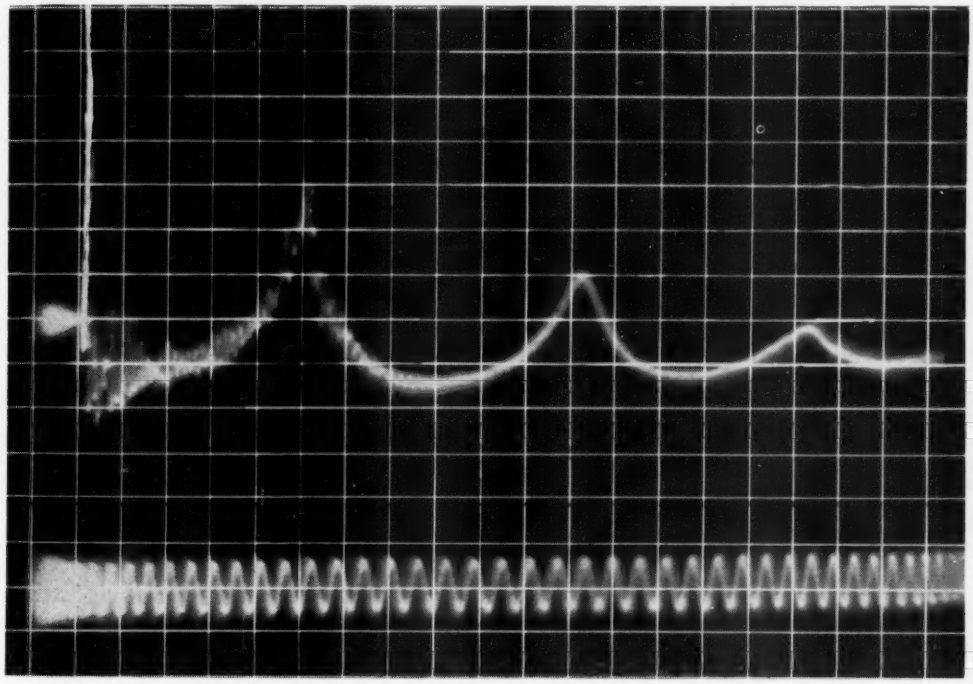

Fig. 6.—A record of pressure changes in the tank of water during the shot reproduced in motion pictures of Fig. 7. The first peak at the left is that of the shock wave pressure. The first, second, and third peaks, corresponding to three minimum cavity volumes, are well marked. Note the subatmospheric pressures below the base line. The high frequency (3,000 per second) pressure excursions in the first third of the record are due to vibration of the steel frame of the tank. One vertical division represents 13.1 pounds per inch^2 pressure. The time record is 1000 cycles.

In the human body somewhat similar changes must occur during the passage of a bullet, an increased pressure followed by a decreased pressure. However, mass of material and elastic walls may be expected to modify the movements and the pressures developed. After a shot through the abdomen of a cat, the expansion of cavity to maximum volume occupies much less time than in a large tank of water (see Harvey and associates[11]). The important difference between the water and the abdomen shot lies in cavity behavior after collapse. Microsecond roentgenograms of the cat's abdomen show no second expansion of the

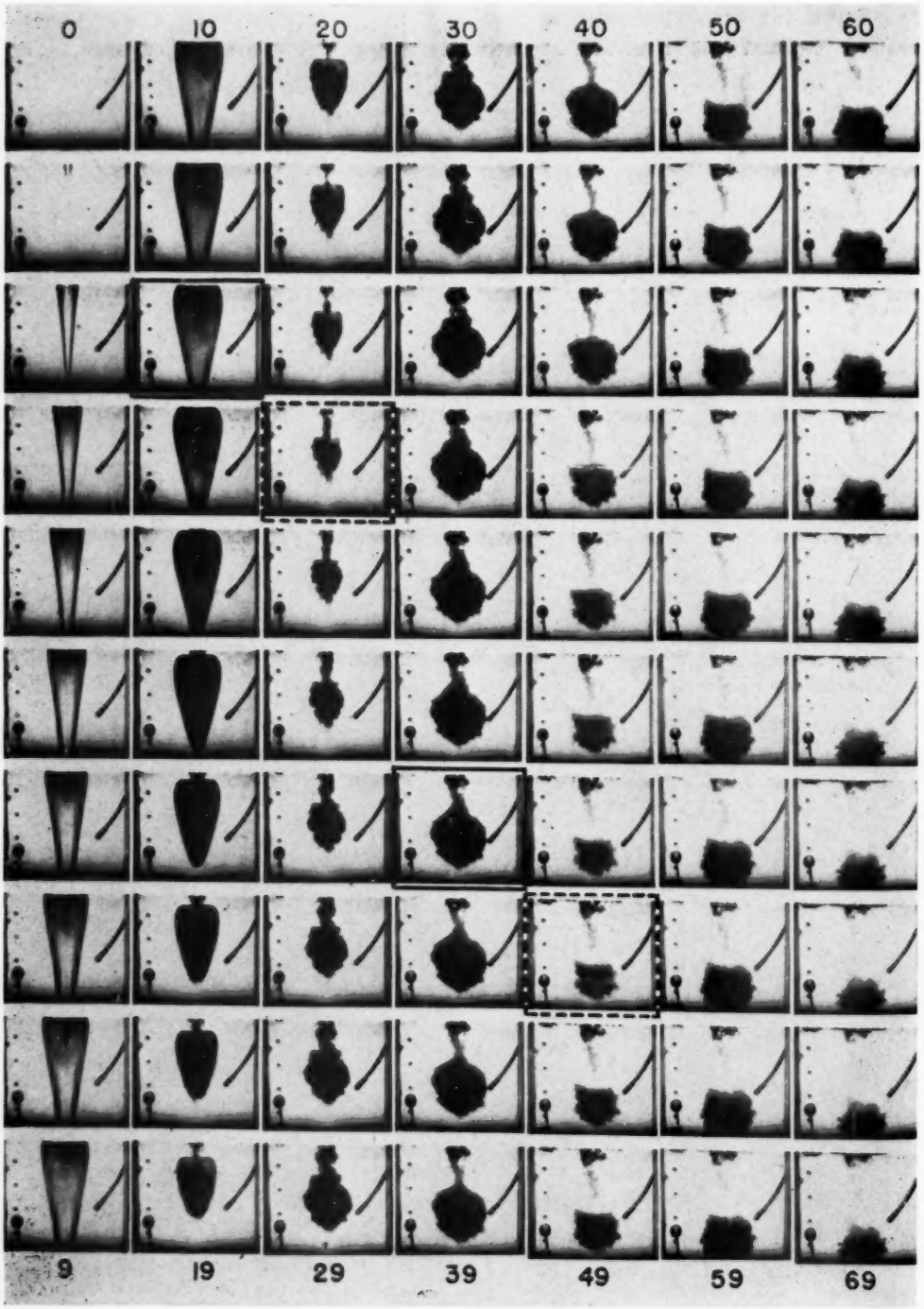

Fig. 7.—Frames from a high-speed (2,120 frames per second) motion picture of a 3/16 inch steel sphere entering a tank of water with a velocity of 3,000 feet per second. The dots to the left are 5 cm. apart. The crystal gauge is visible as the slightly curved line at right. The crystal pressure record is reproduced in Fig. 6 (Experiment 3 of Jan. 18, 1946).

temporary cavity. Because of the small entrance and exit holes in the abdominal wall, air cannot rush into the cavity as in a water shot. The cavity space is filled almost entirely with water vapor and practically complete collapse takes place. The slight oscillations in pressure which occur can be attributed to gas pockets already present in the intestines.

POSSIBLE DAMAGE FROM SHOCK WAVES IN GAS-FREE TISSUE

Possible damage from shock waves will presumably depend on their intensity. The question that concerns us is whether or not the waves generated by small high-velocity missiles are destructive outside the limits of the observed stretching and tearing caused by the temporary cavity. It might be predicted that a mass of tissue suddenly struck by a pressure pulse of 10 to 60 atmospheres, traveling, 4,800 feet per second, would be seriously affected. However, it is well known that hydrostatic pressure itself, even when applied for considerable time periods, does not affect tissues unless the pressure is excessive, greater than 500 atmospheres (see Cattell[12] and Brown[13]). Since shock waves last a very short time and involve only slight displacement of the medium, it is possible that liquid tissue could withstand the slight displacement without damage.

One experiment may be cited to show that even such delicate cells as human red blood corpuscles are not damaged when struck by shock waves. A dilute suspension of corpuscles in Ringer-Locke solution was placed in a steel cylinder, $8\frac{3}{16}$ inches internal diameter, filling it to a depth of 9 inches. A ¼ inch steel sphere was then shot into the water with a velocity of 3000 feet per second. Every corpuscle in the cylinder must have been exposed to the high pressure shock waves generated by the sphere. In addition, many corpuscles were subjected to the agitation and movement accompanying the cavity formation, which blew one-half the blood suspension out of the cylinder. Nevertheless, there was less than 1 per cent hemolysis in the remaining blood, no more than is frequently observed on shaking blood with air.

A further test of shock wave effects on tissues was made by tying frog hearts in various positions in a tank of Ringer's solution and then shooting a steel sphere among the hearts. A high-speed moving picture was taken and the hearts were examined carefully after the shots to determine any change in amplitude or rate of heart beat. The peak pressure pulse that struck each heart could be calculated from the impact velocity and projected cross-sectional area of the sphere and the distance and angle of the heart from point of impact of the missile on the water surface.

In Fig. 8 are reproduced frames from such a high-speed moving picture of a ⅛ inch steel sphere striking the water with a velocity of 3,100 feet per second and an impact energy of 6 times 10^8 ergs. The hearts, tied to vertical strings in Ringer's solution, were beating well before the shot. From the moving picture the exact position of the cavity at all phases of expansion and contraction can be seen.

Some of the hearts (C_1, C_2, C_3) were engulfed by the cavity and either torn loose or damaged so that the beat ceased or greatly slowed. Others (B_1, B_2, B_3) were outside the range of the temporary cavity. Two of these hearts (B_1 and

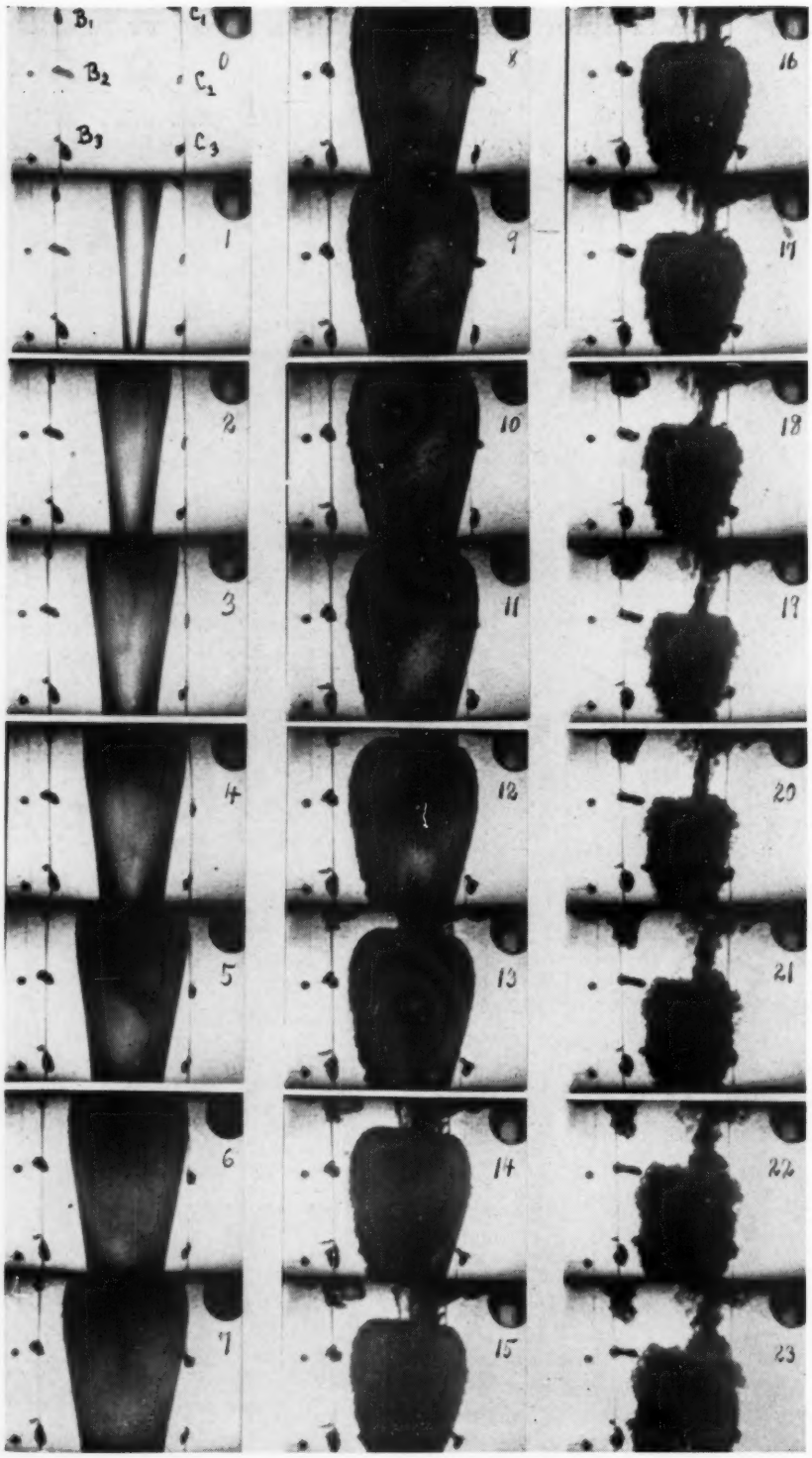

Fig. 8.—Frames (2,400 per second) from a motion picture (168) of six frog hearts tied to two vertical strings in a tank of Ringer's solution. The surface of the water is at the top edge of each frame. A ⅛ inch steel sphere, with impact velocity of 3,100 feet per second, penetrated the solution between the vertical rows of hearts, and the development of the temporary cavity is seen clearly. The effect on the hearts is described in the text. The vertical row of dots on left are 5 cm. apart. The circle in upper left is a mirror reflection of a sodium lamp flashing 120 times a second.

B_3) were unharmed although hit by shock waves whose peak pressures were about 25 atmospheres; the third heart (B_2) was torn and bleeding and its beat slowed. This heart was hit by a 32 atmosphere shock wave but it was also in such a position that rapid radial movement of the water as the cavity expanded and contracted pulled it violently back and forth on its mooring. It is just this same stretching and tearing which must damage tissue around the path of a missile.

The immediate question in this experiment was whether or not it was the shock wave or the tearing which damaged heart B_2. An attempt was made to answer this question by producing high-intensity shock waves without a cavity or with a minimum of cavity formation. If frog hearts subjected to much stronger shock waves in absence of a cavity are unharmed, we may conclude that movement near the cavity was responsible for damage in the previous experiment.

The experiment was carried out by tying frog hearts in position in a tank of Ringer's solution as before, but rigidly supporting on the surface of the water a 1/8 inch thick piece of steel armor plate. This material was then struck with a 1/8 inch steel sphere moving 4,500 feet per second. The steel sphere, with a striking energy of 14.6 times 10^8 ergs, did not perforate the armor plate but produced a small hemispherical blister on its undersurface. Spark shadowgrams showed that a strong shock wave arose from the blister and traveled through the liquid. A small cavity also appeared around the blister and quickly subsided. At its maximum this cavity had a volume of approximately 16.7 c.c. as compared with the 535 c.c. volume of the cavity shown in Fig. 8.

The shock waves from the bulge on the armor plate are shown in Fig. 9. The spherical wave can be seen clearly, as well as the plane waves at an angle of 20 degrees with the plate, which result from elastic waves of the plate. Judging from the width of the absence-of-light band in the spherical shock wave, the peak pressure that struck the hearts (2.5 cm. away from the plate blister) was between 81 and 117 atmospheres. Despite the greater intensity of shock wave, none of the hearts was injured.

Other similar experiments have led to the general conclusion that shock waves from high-velocity missiles do not damage tissues in a completely liquid system. It therefore seems reasonable to conclude that damage to the heart of the previous experiment was not due to the shock wave but to the rapid movement of water caused by expansion and contraction of the temporary cavity.

DAMAGE DUE TO PRESENCE OF GAS POCKETS IN TISSUE

The situation is completely changed when gas is present in tissue. Two of the six hearts suspended under the armor plate and used in the previous experiment each had a bubble of air injected into them with a fine hypodermic needle. The air injection was made some fifteen minutes after the first shot without air injection. This first shot, in which the hearts were not injured, therefore served as a control for the second shot. It was observed that all six (in three different experiments) of these air-injected hearts were injured,

whereas, among a total of seventeen hearts without air injection, exposed to shock waves one, two, or three times, only two were injured and one of these was behaving abnormally before the shot.

Moreover, the nearer the air-injected hearts were to the very small cavity which appeared under the armor plate, the more seriously were they damaged. It was observed in Fig. 10, a high-speed moving picture of the air-injected hearts (marked *A* and *F*), that near the cavity a very marked enlargement of

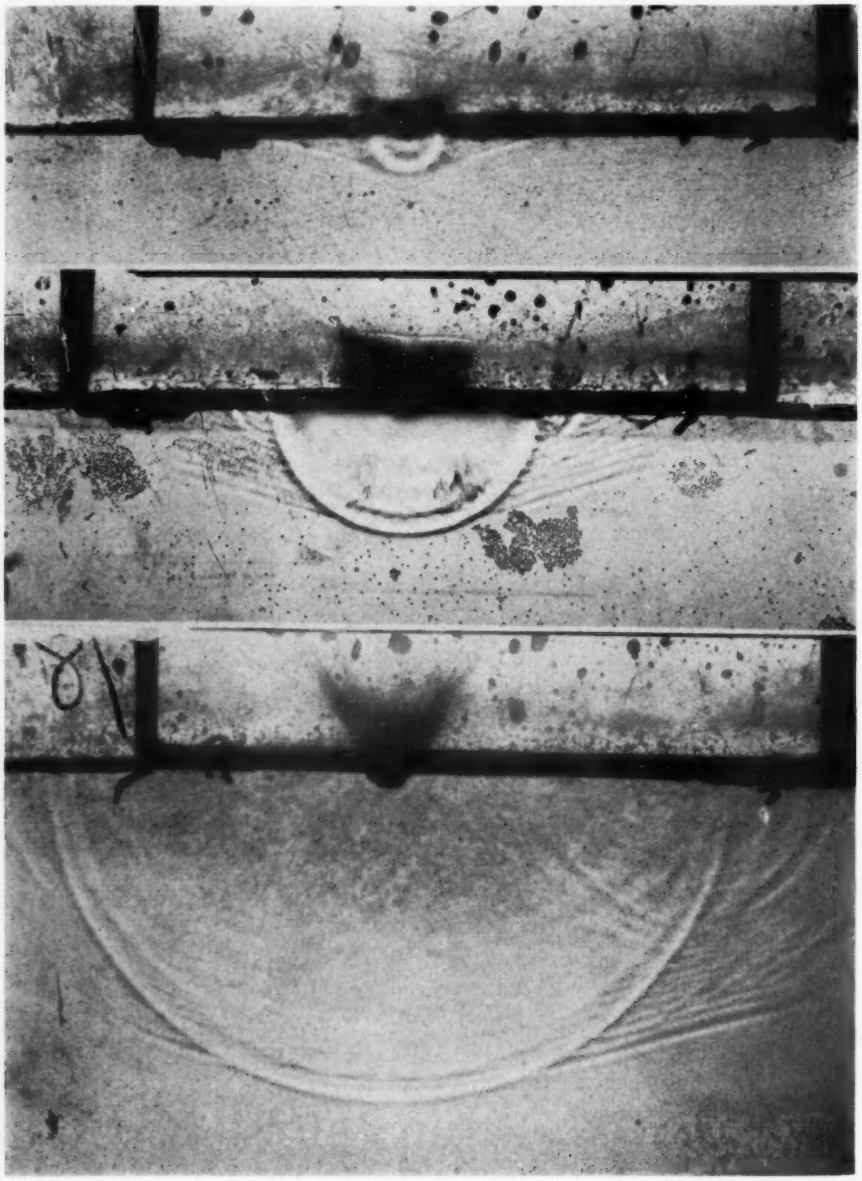

Fig. 9.—Spark shadowgrams (K16, K14, and K18) of the successive movements of a shock wave in water below a ⅛ inch sheet of armor plate. The plate has been struck (without penetration) by a ¼ inch steel sphere moving 4,500 feet per second, and the splash of metal is clearly seen. In addition to the hemispherical wave, elastic waves in the metal pass to the water, making an acute angle with the plate.

heart *A* occurred, due to expansion of the air during the sub-atmospheric pressure phase of cavity formation.

Similar expansion of air-filled balloons also occurred near the cavity, as shown in Fig. 11. Balloon *A*, near but never touched by the growing cavity, actually expanded to the bursting point and also affected its neighbor, *C*, below to the left. Balloon *D*, on the other hand, only 6 cm. away from the maximum limit of the cavity, was not affected. Balloon *C* received a very strong shock wave, the effect of whose pressure is just perceptible in its slightly smaller size in Frame *1* as compared with frame *0*.

Such experiments as are recorded in Fig. 11 give very conclusive evidence that subatmospheric pressures connected with cavity behavior are the cause of destruction in tissue. A comparison may be made with the bursting of the balloon membrane.

SECONDARY DAMAGE TO INTESTINES

Perforation of the intestine is one of the important consequences of injury from underwater blast and is also observed well away from the bullet track after shots through the abdomen of anesthetized cats. Roentgenograms show that the cat intestine contains numerous gas pockets. An experiment was therefore set up in the tank to imitate the conditions of an abdominal shot and particularly to observe what happens to a gas pocket in the intestine. A segment of cat's colon and a small part of the ileum were removed, thoroughly washed with saline solution, filled with Ringer-Locke solution, and the ends tied off, leaving a large bubble of air within. It was suspended in a tank of Ringer-Locke solution in the form of a ring, with the ligatures tied together, and the bubble of air so manipulated that part of the air remained near each end. A 1/8 inch steel sphere moving about 3,100 feet per second was then shot into the water through the center of the intestinal loop without hitting any part of the tissue, and a high-speed moving picture of the changes was taken.

Frames from this picture are reproduced in Fig. 12. The position of only one air bubble shows well, that at the right end of the intestine. In Frame *1* the cavity from the shot is quite marked and it will be observed that the air in the bubble is compressed, as indicated by the narrower right end of the intestine. In Frames *2*, *3*, and *4* the right end of the intestine is expanding and the outline of the bubble is clearly visible. The temporary cavity behind the sphere is still expanding rapidly. In Frames *5*, *6*, and *7* the bubble again contracts and later undergoes less marked form changes which are quite comparable to the balloons of Fig. 1.

When examined after the shot it was observed that the colon was intact except for a small cavity in the mucosa and submucosa over the bubble. The muscularis layer in this area appeared blistered and wrinkled, having been considerably stretched, but it was not perforated. The contents of the gut, originally clear, had become turbid, presumably because of tissue loosened by agitation and stretching.

Greatest movement in the intestine occurred around the air bubble, whose diameter nearly doubled between Frames *1* and *3*. This means a volume increase

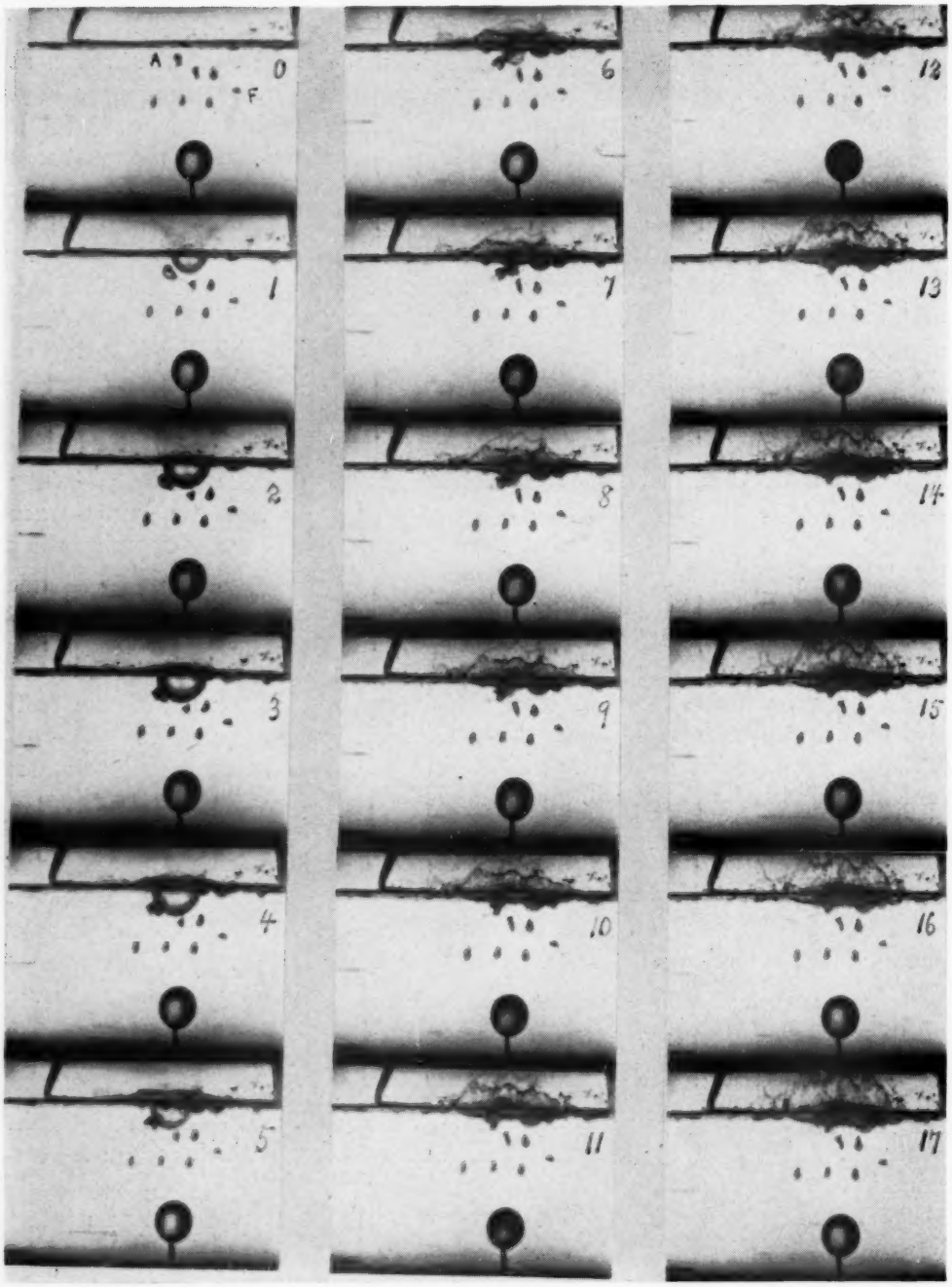

Fig. 10.—Motion picture (SW5) frames (about 2,000 per second) of six frog hearts tied to horizontal strings (invisible) below a sheet of armor plate, which has been struck (without penetration) by a ¼ inch steel sphere moving about 4,500 feet per second. A small cavity appears under the plate in Frames *1* to *6*. The hearts at the upper left and lower right contain air and the expansion of the air in the heart at the upper left is clearly visible. The effect on the hearts is described in the text. The horizontal lines on the left are 5 cm. apart. A circular mirror in the lower middle of each frame reflects a sodium lamp flashing 120 times a second.

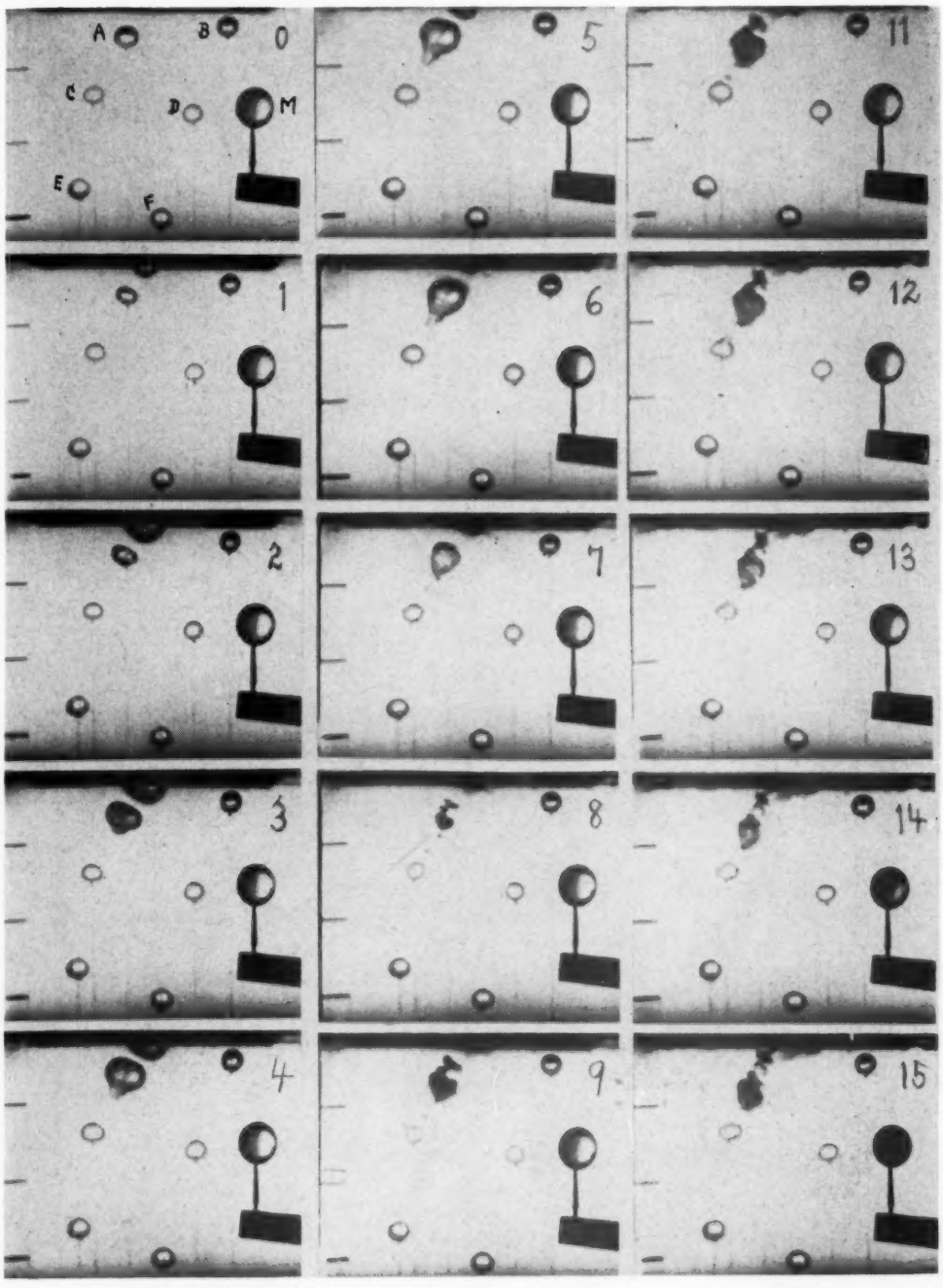

Fig. 11.—Motion picture (191L) frames (about 2,000 per second) of small rubber balloons filled with air and suspended under armor plate which has been hit by high-velocity sphere. Conditions are the same as shown in Fig. 10. The expansion and bursting of the balloon at the upper left as the small cavity under the armor plate approaches is clearly seen. In Figs. 10 and 11 is illustrated how expansion of gas pockets in the body can stretch and destroy tissue. *M*, mirror for timing.

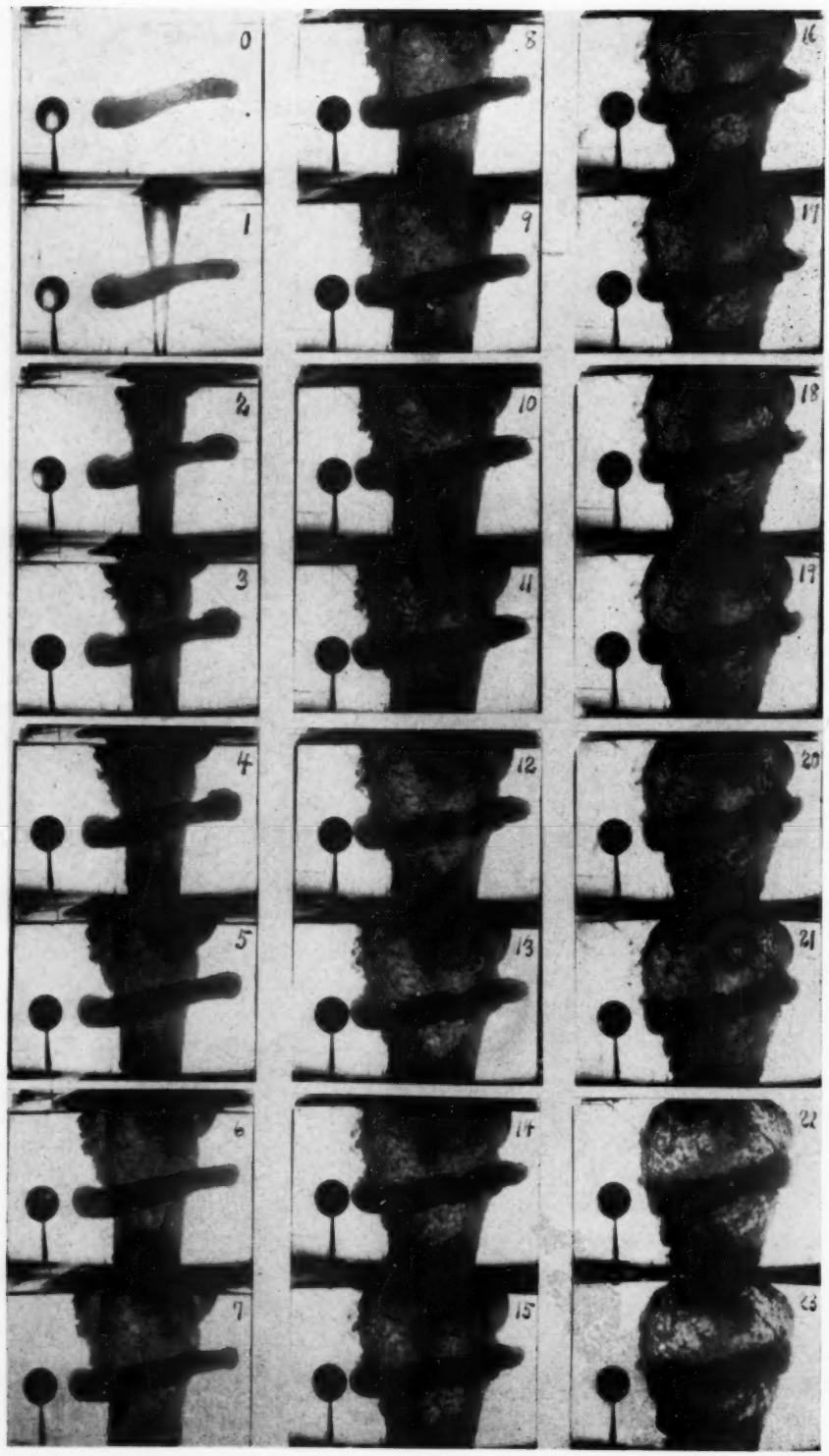

Fig. 12.—Motion picture (173) frames (2,280 per second) of a loop of cat colon with an air pocket in the right end, suspended in a tank of Ringer's solution. A ⅛ inch steel sphere with a velocity of 3,100 feet per second entered the water and passed through the center of the loop of colon without hitting it. The large temporary cavity can be seen to expand and touch the colon. Note especially the slight constriction of the air pocket in Frame *1* and its expansion in Frames *2* to *5*. The distance between horizontal lines at the left is 5 cm.; the timing mirror is also at the left of each frame.

of eight times in less than one millisecond, since the pictures were taken at 2,280 frames per second. It is not surprising that this rapid stretching should do considerable damage.

The important point which is brought out by the heart and intestine shots is that the stretching is not due to the shock wave proper or to the expanding cavity behind the missile but is due to the expanding air pocket already present within the tissue. The air pocket responds to pressure changes around the temporary cavity and the stretching occurs as a result of subatmospheric pressures clearly visible in the pressure record of the tank of water in Fig. 6. Consequently the damage is to be ascribed to the relatively small long-lasting (measured in milliseconds) pressure changes rather than the short (measured in microseconds) high-pressure pulse of the shock wave.

It is true that the shock wave pressure causes initial contraction of the air mass. When subatmospheric pressure appears the gas springs rapidly from a small to a large volume, thereby causing more rapid stretching, but the fundamental cause of injury is due to great extension of tissue. Pressure change per se does not injure. The displacement of tissue accompanying the shock wave generated by impact of high-velocity steel spheres is invisible in a moving picture and too small to do damage. The displacement from expansion of a gas pocket is readily observed and the damage is comparable to primary damage connected with the temporary cavity.

Where shock waves are enormous, as from underwater explosions of hundreds of pounds of TNT, the displacement in tissue due to the shock wave might be sufficient itself to cause damage. However, the subsequent low pressure around the explosion bubble also extends long distances from the explosion and it may very well be that damage to personnel from underwater explosions is directly connected with the expansion of gas in lung or intestine by this low pressure component. It must also be remembered that whenever a shock wave is reflected from an air surface it is inverted and becomes a low-pressure wave. The reflected wave could also be the important factor in causing damage.

SECONDARY DAMAGE TO LUNG TISSUE

Lung hemorrhages occur in personnel injured by underwater explosions. It is not surprising to find that sudden expansion of gas in the alveoli so stretches the walls as to break small blood vessels. No experiments have been carried out to demonstrate damage to lung tissue by a shot in a tank of water, but the report of Daniel[14] of severe lung hemorrhage from gunshot wounds of the skin of the chest is a case in point.

DAMAGE TO FISH FROM EXPLOSION AND GUNSHOT

It is well known that fish are particularly sensitive to underwater explosions and can be obtained with little injury by detonating small charges near them. Moreover, hunters have observed that a shot into water near a fish will stun it even though there is no direct hit. The fish lose their power of maintaining equilibrium and are soon found floating at the surface.

Possibly the reason fish are particularly sensitive to explosions is again to be sought in their possession of a swim bladder, a mass of gas which is rapidly expanded and injured by the subatmospheric pressure accompanying the cavity formation. We have endeavored to test this view on fish with swim bladders.

In one experiment guppies (about one inch long) were tied to supports in the water and a ⅛ inch steel sphere moving 3,100 feet per second was fired among them. All of these delicate fish were killed, although none of them was in the bullet path and many were far removed from the maximum extension of the temporary cavity.

Attempts were made to test this idea further with small goldfish (two inches long) which also possess a large swim bladder connected with the pharanx. By placing goldfish in water under a partial vacuum, the gas of the swim bladder expands and some escapes through the mouth. Roentgenograms of such fish were taken before and after the vacuum treatment to find out how much gas remained. These roentgenograms indicated that the gas volume can be reduced considerably.

Goldfish with a large (before evacuation) and a small (after evacuation) amount of air in the swim bladder were then placed in large mesh hair nets and held in similar positions around the path of a high-velocity shot (⅛ inch steel sphere moving 3,100 feet per second) into water to see if those fish with little air in their swim bladders were unharmed. Because of variability among the fish these preliminary results were inconclusive, although there was some evidence of protection after removal of most of the swim bladder gas. The press of other matters has prevented continuation of these experiments and they should be repeated and extended. It should also be determined whether fish lacking swim bladders (elasmobranch) are immune to secondary explosion damage while those possessing them are particularly sensitive. Enough evidence has been presented to demonstrate the part played by air pockets in wounding.

SUMMARY

Primary damage in wounding results from direct crushing of tissue in front of the moving missile and from stretching and tearing in a wide region around the missile path. The stretching results from the formation of a large temporary cavity behind the missile which leaves a region of extravasated blood on collapse. The cavity formation is explosive in character and a comparison is drawn between a shot into tissue and an underwater explosion.

Secondary damage occurs only if gas is present and results from the effect of pressure changes accompanying the passage of a missile through tissue on the gas. The pressure changes are of three kinds: (1) shock wave pressures that originate when the missile strikes and that move through tissues with the velocity of sound in water; (2) a high pressure region around the moving missile; (3) pressures, both positive and subatmospheric, connected with the behavior of the temporary cavity.

The events which occur during a shot into a tank of water are similar to those in tissue. Hence, an analysis has been made of the cause of damage by

suspending tissues or organs in salt solution and shooting among them. Blood corpuscles, frog hearts, and intestinal loops were used.

Damage occurs in gas-free organs only if the tissue is severely stretched by movement of the temporary cavity. When gas is present in an organ, secondary damage results from expansion of the gas as a result of the subatmospheric cavity pressure. The expanding gas pocket stretches tissue in a manner quite similar to that of the temporary cavity. Fish in water are peculiarly sensitive to damage from gunfire or detonation because of their swim bladders.

The high pressure of shock waves resulting from impact of missiles does not appear to cause damage; rather, it is decreased pressures that are destructive. Such decreased pressures occur when a shock wave is inverted by reflection from an air surface. In this case the low pressure shock wave can damage. Injury to men in underwater blast probably results from the reflected wave.

ACKNOWLEDGMENT

We take pleasure in thanking Mr. Joseph Gonzalez for help with the photography.

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THE TREATMENT OF ACUTE APPENDICITIS SUPERIMPOSING SEVERE EXOPHTHALMIC GOITER

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REPORTED cases,[1, 2] of exophthalmic goiter complicated by acute abdominal surgical disease have been but few. On the other hand, writers[3-7] have frequently stressed the importance of differentiating that group of abdominal symptoms of hyperthyroidism, such as acute attacks of nausea, vomiting, and pain, which most often simulate acute cholecystitis or acute appendicitis, from actual concomitant acute surgical disease of the abdomen.

In the latter cases the abdominal symptoms are due entirely to overactivity of the thyroid gland, and emergency surgery which is not necessary may lead to disastrous results. Yet failure to recognize and treat properly a concomitant acute appendicitis requiring immediate surgical care may be equally disastrous. Difficulties in differential diagnosis between these two abdominal conditions may at times be insurmountable and clinical differentiation is not always possible. When adequate therapy is applied in hyperthyroidism uncomplicated by an intra-abdominal lesion, the abdominal symptoms usually disappear with other signs of toxicity.

In the acute abdominal cases the signs and symptoms usually progress. Moreover, with a concomitant lesion such as acute appendicitis, all of the symptoms and signs of hyperthyroidism may become progressively more severe so that the patient may at times develop a thyroid crisis. A precrisis state is often reached, such as that presented by the patient described here, which requires extra preoperative and postoperative care to prevent a thyroid crisis and a fatal issue. In the treatment of this patient the methods set forth in another communication[8] were followed.

CASE REPORT

A. C., (No. 427847), a white housewife 39 years of age, was admitted to the University Hospital on Sept. 12, 1942, at which time there was all evidence of acute appendicitis of four hours' time which had superimposed known exophthalmic goiter of four months' duration.

There was a history at that time of gradual development of a goiter and of nervous irritability since April, 1942, associated with tachycardia, palpitation, emotional instability with easy crying as well as anger without due provocation, decreased tolerance to heat, increased sweating, easy fatigability, muscular weakness, and much loss of weight of from 180 to 135 pounds in spite of a voracious appetite. She claimed these symptoms occurred in attacks which lasted for days without remission and even interfered with sleep. They progressively became worse until July, when they were accompanied by abdominal cramps, nausea, and vomiting. At this time she consulted the local physician who diagnosed toxic goiter. Since 1930 she had several such attacks but much milder with spontaneous remissions. They required no treatment. A basal metabolic rate as determined by the local physician in July, 1942, was increased. He advised thyroidectomy. The symptoms were not relieved by Lugol's solution administered by the physician up to one week before admission.

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During this admission she complained principally of an attack of epigastric cramps which occurred at noon, September 12. It was soon followed by nausea and vomiting. Two hours later the pain localized in the right lower quadrant of the abdomen.

Physical examination revealed the temperature was 103.4° F., with the pulse 120, respirations 22, and the blood pressure 160 systolic and 90 diastolic. Abdominal examination showed tenderness with slight spasticity in the right lower quadrant over McBurney's area. There was also slight tenderness in the right flank. Rebound tenderness was referred to McBurney's area. The rest of the examination revealed a marked restlessness. The thyroid was moderately and diffusely enlarged. There was moderate exophthalmos. A fine tremor of the protruded tongue and of the extended fingers was present. The face was flushed and the skin warm and moist. Tachycardia, increased pulse pressure, and fever were great. The white blood count was 11,000 with 88 per cent neutrophiles and 12 per cent lymphocytes. The urinalysis was negative.

There was an exaggeration of all thyrotoxic symptoms with pending thyroid crisis due to an acute retrocecal appendicitis. Rigorous treatment to prevent thyroid crisis was immediately instituted including adequate sedation, parenteral administration of Ringer's solution with 5 per cent glucose and 500 mg. of iodine as potassium iodide. Emergency appendectomy was performed, September 12. Under avertin, 80 mg. per kilogram, and cyclopropane, oxygen, and helium anesthesia, the abdomen was opened through a Battle pararectus incision. An acutely inflamed appendix was found retrocecally, which was removed. It was gangrenous up to 1 cm. from its base. The stump was treated with phenol and alcohol.

It was not inverted but completely covered with a portion of the mesoappendix. Ten grams of sulfathiazole powder were placed about the appendical area. Microscopic examination revealed acute diffuse suppurative appendicitis with areas of gangrene (Fig. 1).

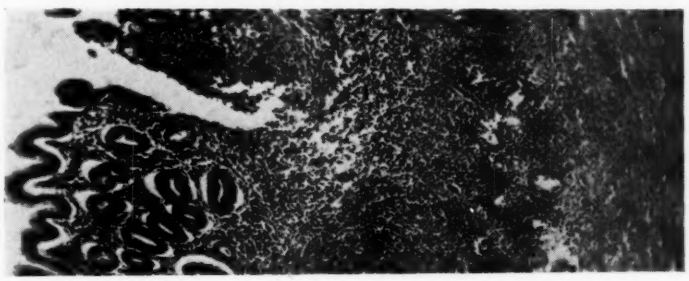


Fig. 1.—Acute suppurative appendicitis. Note the area of necrosis of the mucosa and the polymorphonuclear cell infiltration of the depths of the appendix.

Immediately following the operation the preoperative measures were continued. Oxygen was administered by intranasal catheter. The body temperature was controlled by an ice-cooling system which consisted of placing over the lower extremities wet towels covered with ice over which air from an electric fan was blown. Morphia, ¼ gr., was given every four hours as long as the respirations were 16 or above. The patient was kept in a semi-Fowler's position. The cooling system was discontinued in a few hours. The postoperative temperature reached its peak of 101.2° F. on the first day with the pulse 118 and respirations 24. It gradually returned to normal on the third day, where it stayed thereafter. Sips of water and food were given as soon as tolerated. Two hundred milligrams of iodine as well as a high carbohydrate, high protein, high calcium, high phosphorus, and high vitamin intake were given daily. Recovery was uneventful.

The basal metabolic rate determination on the tenth day, September 22, was plus 22 per cent with the pulse rate 64 and the respirations 11. She was discharged on September 27, the fifteenth day, as improved to return in one month for thyroidectomy. She was advised to continue bed rest, sedation, and a high caloric, high vitamin, high calcium, and high phosphorus diet for a period of one month, during which iodine was discontinued. She

felt well for one week after discharge. Then she began to notice a return of all of the thyrotoxic symptoms. These symptoms became progressively worse until readmission on Oct. 28, 1942. Weight had remained stationary at 135 pounds.

Except for this present illness, general health was good. A left otitis media developed in 1920 with spontaneous rupture of the drum. The upper teeth were all extracted years before because of dental caries. She had short periods of amenorrhea since 1930. Dizziness and frontal headaches occurred occasionally.

Family history revealed no positive findings. She knew of no goiter in the family.

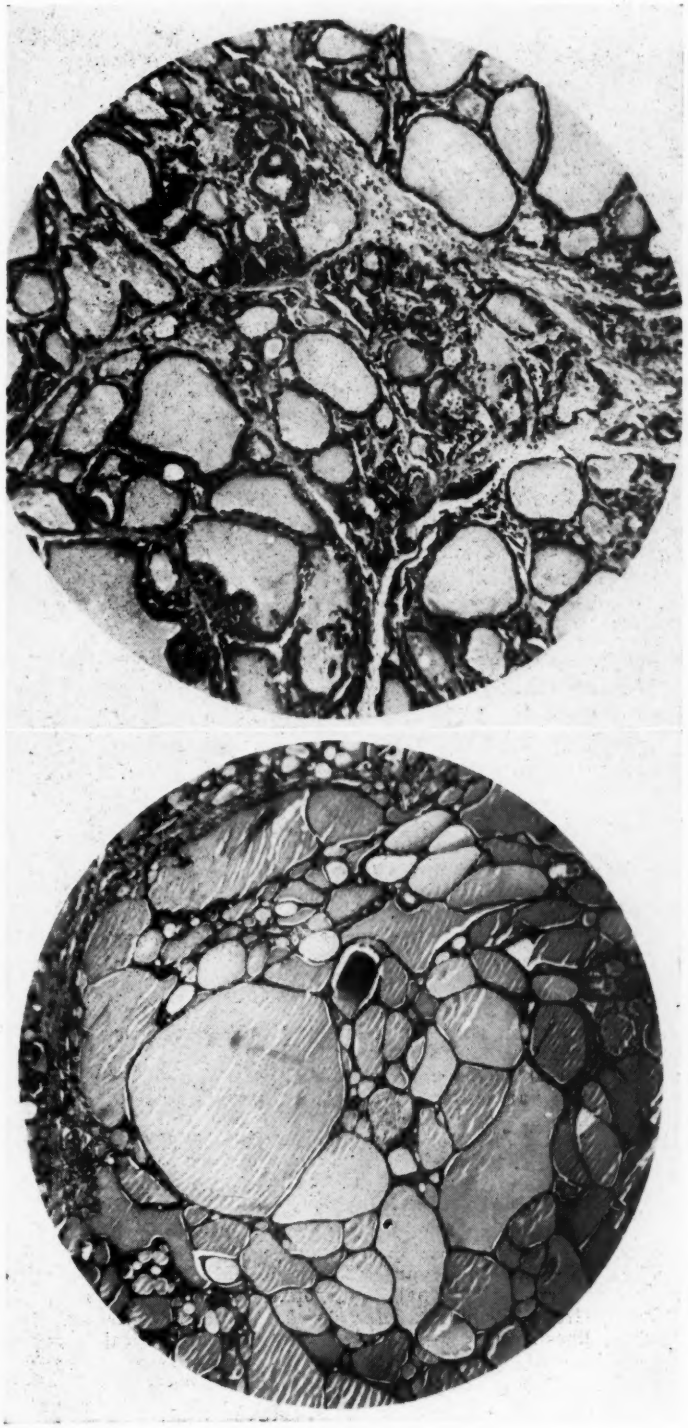
Physical examination revealed a well-developed and fairly well-nourished white woman whose facial expression was that of frozen terror. Temperature was 98.6° F. with the pulse 140, respirations 28, and the blood pressure 162/90. Face was flushed. Skin was warm and moist. There was marked exophthalmos bilaterally with exophthalmometric readings of 23 mm. on the right and 21 mm. on the left. A widening of the palpebral fissures was demonstrable. There was a lag of the upper lids as the eyes followed the finger downward. Difficulty in convergence was present. Pupils were regular, equal, and reacted well to light and accommodation. The fundi were normal. Hearing was good and the drums intact. There were no nasal abnormalities. She wore a full upper dental plate. The protruded tongue showed a fine tremor. The oropharynx was clear. Indirect laryngoscopy showed the vocal cords normal in appearance and their function good. The neck veins pulsated rapidly and vigorously. There was moderate diffuse enlargement of the thyroid gland. This moved on deglutition. A thrill was palpable and a bruit was heard by auscultation over the gland. Chest and breasts were well developed. Lungs were clear to percussion and auscultation. Heart was not enlarged, its sounds were of good quality, and its rate was rapid but regular. No murmurs were heard. Abdomen showed a well-healed right rectus scar. The abdominal wall was soft and not tender. The liver, spleen, and kidneys were not palpable. No masses were found. Pelvic examination disclosed a moderately eroded cervix. The uterus was anteflexed, nodular, and slightly enlarged. Rectal examination revealed small external hemorrhoids. There was a fine tremor of the extended and abducted fingers. The extremities were otherwise normal. Reflexes were slightly hyperactive.

Red blood count at time of admission was 4,770,000 with the hemoglobin 14 Gm. per cent. The white blood count was 5,500 with neutrophiles 53 per cent, lymphocytes 45 per cent, and monocytes 2 per cent. Urinalysis was negative. Blood Wassermann and Kahn reactions were negative. Blood urea nitrogen was 15 mg. per cent. The basal metabolic rate was plus 64 per cent with the pulse 144 and respirations 18. The total blood iodine was 13.26 μ per cent and the organic fraction 2.6μ. per cent, which are definitely increased. An electrocardiogram revealed sinus tachycardia and slight left axis deviation. Fluoroscopy and anteroposterior as well as lateral roentgenograms of the neck and chest revealed anterior displacement of the trachea. The lung fields were clear and the heart as well as the aorta appeared normal.

A regimen of adequate bed rest, adequate sedation, and a high calcium, high phosphorus, high vitamin, and high caloric diet was followed. The diet was supplemented with dical-D wafers, five daily, for the first fourteen days. On this regimen the basal metabolic rate decreased gradually to plus 40 per cent on November 10 with the pulse 116 and respirations 18. One hundred milligrams of iodine as potassium iodide were given daily beginning on November 12. The basal metabolic rate further decreased to minus 1 per cent with the pulse 96 and respirations 12 on November 24. On this regimen all thyrotoxic symptoms gradually decreased in severity. The patient became generally composed, comfortable, and at ease. There was a gain of weight. She was therefore considered ready for bilateral subtotal thyroidectomy. Morphia, $\frac{1}{6}$ gr., and scopolamine, $\frac{1}{200}$ gr., were given preanesthetically. Usual skin preparation with tincture of merthiolate and usual draping were made.

Under avertin, cyclopropane, ether, and helium anesthesia, a high collar incision was made. The upper and lower flaps were then dissected back and a midline incision was carried down to the isthmus of the thyroid, thus separating the strap muscles. The right lobe of the thyroid was then exposed and found to be moderately enlarged and principally extended retrotracheally. There was no evidence of nodularity. The left thyroid lobe was

A.



B.

Fig. 2.—*A*, Exophthalmic goiter. Alveoli are irregular in size, contain a small amount of colloid, and the epithelium is hyperplastic in character with a few papillary projections present. *B*, Exophthalmic goiter. Small areas of involution such as this were found rarely.

exposed, which was diffusely enlarged. A large part of this lobe was also retrotracheal in position. It was delivered. The upper pole, and then the lower pole, were clamped, divided, and ligated in the usual fashion. The lobe was subtotally excised, using a modified Halsted technique. The right lobe was similarly excised. A pyramidal lobe was totally removed. About 5 Gm. of the posteromedial portion of thyroid gland was left bilaterally. Usual saline irrigation and complete hemostasis using black silk were carried out. Closure was made in the usual fashion using black silk throughout and no drainage. The immediate postoperative condition was excellent.

The thyroid gland as removed weighed 45 Gm. and measured 6 by 2 by 2.5 cm. It was diffusely enlarged, friable, and vascular. On cut section the surface was beefy and uniform in consistency. The amount of colloid appeared minimal. Microscopic examination showed diffuse hyperplasia (Fig. 2, *A*) with few areas of hyperinvolution of the acini (Fig. 2, *B*).

Final diagnosis was genuine exophthalmic goiter.

Postoperatively the patient was placed in a semisitting position. An ice collar was tied about the neck. Fluid and mineral balance were maintained by parenteral administration of Ringer's solution with added 5 per cent glucose and 200 mg. of iodine as potassium iodide. Sips of water were allowed as desired and a rapidly increasing diet was given as tolerated. One hundred milligrams of iodine as potassium iodide were given by mouth on the second day and daily thereafter. The postoperative course was smooth. The temperature reached its peak of 101.2° F. on the first day with the pulse 132 and respirations 22. They rapidly receded and remained normal after the third day. There was never evidence of parathyroid tetany or of recurrent nerve injury. Alternate skin stitches were removed on the second day and the remainder on the fourth day. She was discharged as improved on the fifth day, Nov. 30, 1942.

She was seen by me on Jan. 5, 1943, at which time the basal metabolic rate was plus 3 per cent with the pulse 80, respirations 18, and blood pressure 140/84. She had taken one tablet of iodine (about 10 mg. of iodine) once daily during the interval. There was a gain of weight to 150 pounds and she felt fine. The scar was minimal. The patient was discharged as recovered, to return if symptoms recurred.

SUMMARY

This case is set forth as presenting a rare complication of exophthalmic goiter. It also emphasizes the minimal postoperative reaction which may occur following emergency appendectomy in the presence of severe exophthalmic goiter.

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MALIGNANT SOFT TISSUE TUMORS OF THE LOWER EXTREMITIES: A RADICAL-CONSERVATIVE TECHNIQUE OF WIDE EXCISION AND SKIN GRAFTING WITHOUT AMPUTATION

Report of Five Cases

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THE purpose of this discussion is to present a method for dealing surgically with certain malignant tumors involving the soft tissues of the lower extremities. This method can be termed a radical-conservative technique: radical in that such an extensive excision is done that large skin grafts are necessary; conservative in that amputation is not performed. It should be stated definitely at this time that we are not advocating this technique as a substitute for amputation nor do we believe that it will give as high a percentage of cures as will amputation. It is, however, indicated in certain cases, particularly when amputation is refused, and is in all instances preferable to a conservative local excision. While the method may be applied in selected cases to any type of malignant neoplasms, it is felt that it can best be used for the slow-growing types of sarcomas. The lower extremities have been chosen for two reasons. The first is that tumors involving this region may be evaluated more accurately concerning their local growth and the infiltration of surrounding tissues, and their regional metastases may be demonstrated more easily. The second is that in all patients upon whom this method has been carried out the location of the tumor was on the lower extremity and the patients with such lesions are often unwilling to have amputation. Since these cases were reported, this technique of radical excision and skin grafting has been applied* to a superficial sarcoma of the left forearm in a 32-year-old man. Two of our patients refused amputation. The group of slow-growing sarcomas such as the fibro-, myxo-, and liposarcomas make up a relatively small group of malignant neoplasms. However, because they are slow growing, infiltrate locally, and are slow to metastasize, they lend themselves to surgery with potentially very gratifying results; and it is upon these characteristics that the method to be presented here, of very wide excision with extensive skin grafting, is based.

Nothing can be added to the pathologic description of sarcomas as a whole by Ewing[1] and Warren and Sommer.[2] These tumors, in general, are thought to be derived from connective tissue or mesothelial elements. Their cells are laid down upon an abundant vascular network which gives them a highly vascular gross appearance. They may grow quite rapidly, such as either Ewing's or osteogenic sarcomas, or they may grow slowly as does the group with which we are chiefly concerned. If their course is uninterrupted they may reach very large proportions, and when doing so they frequently ulcerate or their centers become necrotic. With the exception of lympho- and melanosarcomas they are thought to metastasize via the blood stream and rarely do they involve regional lymph nodes. However, it was more recently claimed by Ewing,[1] and by Meyer-

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*By Dr. Bruce Franz.

ding, Broders, and Hargrave,[3] that the regional nodes are involved more frequently than had heretofore been thought, and an incidence of such involvement of 3 to 12 per cent was reported by various authors in the literature. The tumors usually appear to have a capsule which, however, has been shown in most instances not to be a true one because tumor cells may be found in the surrounding tissues. On cut section sarcomas are usually highly cellular, and may be quite firm or soft. Microscopically they present many different cell types. In a series reviewed at the Johns Hopkins Hospital from 1935 to 1945 there were 8 fibrosarcomas, 2 fibromyxosarcomas, 3 neurogenic fibrosarcomas, 1 fibromyxochondroma, 1 spindle-cell, 1 myxo-, 1 macrophage, 1 rhabdomyomyxo-, 1 round-cell, 1 mixed cell, and 1 undifferentiated sarcoma. Warren and Sommer[2] stated that the presence of giant cells is of value in determining the patient's prognosis, while Carroll and Martin[4] in their series found this to be of no significance. The tumor cells frequently are seen invading blood vessels, and they tend to extend along the fascial planes.

The idea of radical-conservative therapy in the treatment of malignancies of the lower extremities is not unique here. Phemister,[5, 6] of the University of Chicago Clinics, has written extensively upon minimal surgery of bone tumors involving the long bones. He reported excision of even the highly malignant Ewing's or osteogenic sarcomas followed by bone grafting with excellent results. His cases, however, were highly selected and only the patients in whom a very early diagnosis was made were treated in this manner. It would seem that soft tissue tumors would be far more amenable to radical-conservative therapy than would those involving bone. The fact that they are more cutaneous, and make themselves apparent early, enhances an early diagnosis which is essential to favorable results with any type of treatment.

There is some difference of opinion as to the proper method of treating such neoplasms. The tendency is toward local excision although amputation is advised by some. Bick[7] advocated local excision, to be followed by amputation if there were a recurrence. It would seem that due to the relatively benign characteristics of the tumors a wide local excision would be the treatment of choice. The method employed here is based upon these characteristics and is as follows:

Technique.—An incision is made about the tumor in such a manner as to include a very wide margin of skin. The greater width should be proximal to the tumor in line with the direction in which metastasis might take place. It is important to remove a wide margin of skin, especially when excising such tumors as melanosarcomas or others which might actually involve the skin. The incision should extend through the subcutaneous tissue and an even larger area of fascia should be removed. If the tumor involves the muscles, those groups of muscles should be ablated to an equally radical degree. It is particularly important to remove a sufficient area of fascia, because it is along this structure that extension of the tumor tends to take place. If at any time during the procedure there is doubt in the mind of the operator as to whether or not total extirpation of the tumor-bearing tissue is being carried out, a frozen section is of value in confirming this. If it is found that such structures as the

sciatic nerve or great vessels are intimately involved in the tumor, amputation is indicated. Since a large area of skin has been excised, it must of necessity be replaced with a skin graft. As with any plastic procedure this may be done at any time, but the optimal time is at that of the initial procedure because then the wound is fresh and free from infection. Probably the ideal type is the split-thickness dermatome graft because a large area of skin may be obtained with relative ease. Furthermore, the introduction of the dermatome in 1939 has enabled the general surgeons who treat the majority of these tumors to use this technique more readily. In most cases a dissection of the inguinal glands is probably unnecessary. However, if the tumor is one of those which not infrequently metastasize to this region, then this additional procedure should be performed. Postoperative x-ray therapy upon most of these lesions is of little value.

The cases of soft tissue, lower extremity sarcomas reported at the Johns Hopkins Hospital during the ten-year period from 1935 to 1945 have been reviewed. Only those cases which were proved by biopsy were selected and a total of twenty-two were found, exclusive of the cases reported in detail in this paper. The follow-up is of small value because there is little information in most of the records after the patients were discharged from the hospital. However, there are points of interest in the series which will be discussed briefly. In Table I it is noted that the oldest patient was 74 years of age, the youngest 10, and the average 48.2 years. Fifty per cent were between the ages of 40 and 60 years, 10 were males and 12 females, and 19 were white while only 3 were colored. It will be noted that there is a wide variety of types which have been previously listed. It should be emphasized that these tumors are not difficult to diagnose and in all but five cases the preoperative diagnosis was sarcoma. One which had progressed very rapidly over a period of less than one month was thought to be a low-grade cellulitis and gave a clinical appearance of the same. It is the general opinion that trauma plays a prominent part in the initiation of sarcomas. However, only four of the patients (17 per cent) in this series presented such a history, three having previously sustained blows, while in one the tumor had developed at the site of a blister. Meyerding, Broders, and Hargrave[3] reported a history of trauma in 32.9 per cent of their cases, while Carroll and Martin[4] had an incidence of only 5 per cent. It is of interest to note that the presence of a mass or swelling of the part was the only symptom present until late in the course of eighteen cases. Initial pain was present in only two cases, numbness was observed in one case in which the tumor involved the sensory nerves, and stiffness in one in which the tumor was in the popliteal fossa in close apposition with the knee joint. The longest duration of symptoms was eight years, while the shortest was one month, and the average duration was about three years. Carroll and Martin[4] showed a definite relation between the duration and percentage of cures. Those patients in whom the tumor had been present for a long time had a much higher incidence of cure than did those in whom the tumor was of short duration. Of the twenty-two cases, eight patients had had previous excisions of which four were multiple. This is in-

TABLE I. ANALYSIS OF TWENTY-TWO CASES OF SOFT TISSUE SARCOMAS OF THE LOWER EXTREMITIES AT THE JOHNS HOPKINS HOSPITAL, 1935-1945

Age incidence	Oldest, 74 yr. Youngest, 10 yr. Average, 48 yr. 50% between 40 and 60 yr.
Sex	Males, 10 Females, 12
Race	White, 19 Colored, 3
Pathologic type	Fibrosarcoma, 6 Neurogenic fibrosarcoma, 3 Sarcoma, 2 Fibromyxosarcoma, 2 Spindle-cell sarcoma, 1 Macrophage sarcoma, 1 Myxosarcoma, 1 Rhabdomyomyxosarcoma, 1 Round-cell sarcoma, 1 Mixed cell sarcoma, 1 Unidentified sarcoma, 1
Preoperative diagnosis	Sarcoma, 14 Benign tumor, 5 Cellulitis, 1
History of trauma	Blow, 3 Blister, 1
Initial symptoms	Presence of a mass or swelling, 18 Pain, 2 Numbness, 1 Joint stiffness, 1
Duration of symptoms	Longest, 8 yr. Shortest, 1 mo. Average, 3 yr.
Location	Thigh, 13 (rt. 8, lt. 5) Leg or foot, 9 (rt. 5, lt. 4)
Previous operation	Excision, 8 (multiple, 3)
X-ray findings	Lung metastases, 2 Excision of adjacent bone, 3
Metastases by physical examination	Enlarged inguinal lymph nodes, 2 Abdominal mass, 2
Operation	Biopsy only, 5 Amputation, 6 Local excision, 11
Postoperative x-ray	11
Duration of cure (6 cases followed)	Round-cell sarcoma, died 5 yr. 3 mo. Fibrosarcoma, living and well 4 yr. Unidentified sarcoma, Fibrochondromyxosarcoma } died 2 yr. Mixed cell sarcoma, died 8 mo. Neurofibrosarcoma, died 20 days after operation of pulmonary embolus

dicative of the fact that inadequate excisions were performed, and it is the desire of the authors to emphasize particularly this point. Frequently the neoplasms appear to be encapsulated and may be shelled out with ease, but tumor cells are left behind in the surrounding tissue and are responsible for the recurrence. It is because of this that the previously described radical excision is recommended. Of the total number of cases, six patients had biopsy only, nine had local excision, and six had amputations. Of the latter six, two had had

previous excisions. Postoperative x-ray treatment was instituted in eleven of the cases, the results of which are not known. The follow-up is quite incomplete. The patient with the round-cell sarcoma lived for five years three months. One with an unidentified and one with a fibrochondromyxosarcoma died at the end of two years, one died on the twentieth postoperative day of a pulmonary embolism, and two were well after four years.

CASE REPORTS

CASE 1.—J. G., a 27-year-old white man, was admitted to the hospital Nov. 29, 1944, stating that four years previously, in 1940, he struck the left leg against the emergency brake of an auto, and about three months later noticed a swelling at the site of injury just below the knee. In eight months it had reached the size of an egg and was incised. The lump remained and grew at a moderate rate until about one year later, when it was three times this size and was excised. Six months later it reappeared and grew more rapidly. About two months prior to admission the ankle began to swell on standing. He had lost no weight.

Fig. 1.—Grafted area on medial surface of left leg, Patient J. G. Final result fourteen months after radical-conservative excision of recurrent fibrosarcoma.

Physical examination showed a multilobular, firm, bluish-red mass on the inner aspect of the left leg elevated 5 cm. above the surrounding surface and measuring 12 by 13 cm. There were two well-healed scars over it. No palpable inguinal lymph nodes were felt. On Dec. 2, 1944, the lesion was biopsied and a pathologic report of fibrosarcoma was obtained. The patient was offered a supracondylar amputation but refused. Thus as an alternative a very wide excision of the tumor mass was performed, removing skin, subcutaneous tissue, fascia, and muscle down to the tibia over the medial and anterior and posterior aspects of the leg from about 20 cm. above the medial malleolus and extending upward about 10 cm. on the thigh. The excised tissue, including the tumor and surrounding normal tissue, weighed 1,075 Gm. The area was so large (118 sq. in. as determined by measuring the tracing with a planimeter) that only about two-thirds of it was covered with three split-thickness dermatome grafts at this time. The postoperative course was uneventful, and six days later the remaining portion was covered with two dermatome grafts in a similar manner. All of the grafts

remained viable, and the patient was discharged on Jan. 6, 1945, with only a few small granulating areas. After that time he progressed very well. There was no evidence of recurrence or metastases when last seen twenty-four months after the operation, and the only difficulty was mild occasional swelling of the leg below the excision when standing for long periods of time.

CASE 2.—M. S. J., a 38-year-old housewife, first entered the Johns Hopkins Hospital on Feb. 18, 1942, with the chief complaint of progressive enlargement of a mole on the inner aspect of the lower left leg. Family history and past history were not remarkable. As far as the patient knew the mole had been present all her life, and in July, 1941, it began to become suddenly larger, until admission on Feb. 18, 1942.

Physical examination showed a hard, bluish, hairless, raised area about 2 cm. in diameter. About it were many similar areas measuring approximately 2 to 4 mm. over a radius of about 5 cm. There were no enlarged inguinal nodes.

Fig. 2.—Grafted area on medial surface of left leg, Patient M. J. Result on twelfth day after excision of recurrent malignant melanoma.

The area was excised and a single full-thickness graft applied. The patient was discharged on March 15, 1942, and the area was healed. The course was uneventful until February, 1945, when she noticed a small dark nodule in the center of the graft. This nodule began to grow rapidly, and several months later a similar nodule appeared in the skin about 10 cm. above the first and then another about 10 cm. above the second. She had lost about twenty pounds in weight.

Physical examination revealed a bluish mass about 4 by 2 cm. in the graft, and two similar lesions 2 by 1 cm., and about 10 and 20 cm., respectively, above the first. Several smaller, moderately firm inguinal nodes were felt. The chest was clear by x-ray examination. The patient refused amputation, and on Oct. 18, 1945, a radical excision and skin grafting were performed. This excision removed the skin, subcutaneous tissue, and fascia over the entire medial aspect of the leg and the thigh to just above the knee. On October 25 a radical excision of the left inguinal glands was performed. The patient was discharged with the grafted area almost entirely healed on Nov. 12, 1945. She had a recurrence proved by biopsy below the grafted area in September, 1946, following which a Callender amputation was done on Sept. 25, 1946. When last seen four months later she showed no sign of recurrence. Although this type of tumor is not suited for this procedure, it was performed only because the patient would not originally agree to amputation.

CASE 3.—W. H., a 51-year-old banker, first entered the Johns Hopkins Hospital on May 29, 1946, with the complaint of a nodule on the inner lower right thigh which had been biopsied elsewhere three days before with the finding of spindle-cell sarcoma. The patient had noted the lump for six weeks. A radical-conservative operation was suggested (after consultation with two other surgeons) and to this the patient readily agreed, so it was performed on June 3, 1946.

An oblique incision was made below the inguinal crease on the right and extending medially and downward for about six inches. Through this incision the inguinal and femoral lymph glands and the entire upper end of the saphenous vein were removed. The lower end of the incision joined a circular excision around the previous wound with a margin of about three inches on all sides. This circular excision was 19 cm. in diameter and was done with the cautery down to and including the muscular fascia. The entire length of the gracilis and sartorius muscles beneath the circular excision was removed in one block with the superficial tissues. At no point was the original wound opened into or were tumor or edematous tissues seen. The femoral vessels lying in Hunter's canal were somewhat exposed by the muscular excision, and lay at the extreme lateral side of the wound. To cover them up, a relaxing incision was then made 11 cm. to the right of the circular wound and the edges of the latter were brought closer together by suturing them to the muscular fascia. The resultant defect was then only 12 by 16 cm. instead of 22 by 19 cm. as it had been before partial closure. A single dermatome graft was then taken from the lateral surface of the right thigh and applied to the relaxing incision and to the circular defect. The relaxing incision had allowed the main flap to be brought over to cover the femoral vessels which had been exposed in Hunter's canal. An elastic compression bandage and a plaster cast were then applied. The specimen showed an incomplete original removal, but no spread of the tumor.

The patient was discharged on the seventeenth postoperative day with the wounds and the grafted areas almost healed. He played golf soon after and when last seen six and one-half months after operation showed no sign of recurrence. There was little loss of function in the right leg and only a slight pitting edema on the inside of the right ankle, but a swelling was not demonstrable on actual measurement.

CASE 4.—D. S., a 15-year-old colored schoolgirl, was first admitted to the Johns Hopkins Hospital on Oct. 11, 1946, complaining of a painful lump on the upper medial aspect of the right calf. This lump had been present for eighteen months, two months before admission had started to grow more rapidly, and one week before admission had begun to discharge bloody material. Examination revealed an ulcerated mass 7 cm. in diameter which protruded 4.5 cm. above the surface.

On Oct. 15, 1946, a fairly radical excision of the mass was performed.* A large elliptical incision was made about the tumor with a two-inch margin below, and a greater margin above. The fascia of the gastrocnemius muscle was removed with the tumor. It was then noticed that there was a 1 by 2 cm. extension of the tumor at the center of the wound into the outer surface of the gastrocnemius muscle, so a portion of the muscle was removed. A dermatome graft was then taken from the opposite thigh and sutured into the defect. At the same time, the right femoral lymph nodes were excised through a separate incision.

The pathologic examination revealed a localized endothelial sarcoma, probably of a radiosensitive type. The femoral lymph nodes showed no metastases. The patient was discharged from the hospital on the fifteenth postoperative day with the wounds and the graft almost entirely healed. She was given roentgen therapy to the right groin (3,000 R) and when last seen three months after operation showed no signs of recurrence, but there was some swelling of the leg below the grafted area.

*By Dr. Bruce Franz.

CASE 5.—E. C., a 36-year-old colored divorced woman clerk, first entered the Johns Hopkins Hospital on Aug. 21, 1946, complaining of a lump on the lateral surface of the right hip of two years' duration. This lump began to grow more rapidly six months before admission, attaining the size of a small orange. The lump had bled slightly for one week, but was painless. It projected about 3 cm. above the skin surface.

On Aug. 23, 1946, the lump was excised* by an elliptical incision, the anterior portion of which lay along the iliac crest. The fascia overlying the gluteus maximus muscle was removed with the tumor. A dermatome graft was applied to the defect, which measured 16 by 10 cm., four months after operation after the contracture of healing had occurred. Small deep grafts were applied to a small unhealed area on Sept. 16, 1946, and the patient was discharged two weeks later.

Pathologic examination revealed a well-encapsulated lump 4 cm. in diameter which showed a structure typical of neurogenic sarcoma on microscopic examination. When last seen five months after discharge the patient showed no sign of recurrence.

COMMENT

It is fully realized that the report of only five patients with such a short postoperative follow-up can lead to few definite conclusions. One of the five patients (Case 2) developed a recurrence and the leg was amputated eleven months after the radical-conservative operation. However, as has been previously pointed out, the general tendency is toward an inadequate local excision of such tumors. Since many of these patients refuse amputation, the choice is often not between radical local excision and amputation, but between radical local excision and conservative local excision. Because of the relatively benign characteristics of local growth and infiltration and late metastasis to other regions of these tumors, and because they are now infrequently deceptive by their false capsules, we wish to point out that local removal will give good results in selected cases and to emphasize that the excision should be sufficiently radical to eradicate all tumor-bearing tissue. When amputation is refused, this technique, properly applied, is sufficiently superior to conservative local excision to make its performance worth the extra time and trouble.

SUMMARY

1. In certain cases of superficial malignant tumors when amputation is refused, an extremely wide local excision with the immediate application of large skin grafts has certain advantages. This method we have termed the radical-conservative method since it does not involve amputation.

2. This technique is the treatment of choice when the patient has refused amputation and may give almost as good results as amputation in so far as a cure is concerned in the management of many malignant tumors, particularly those of lesser malignancy which involve the lower extremities. When vital structures such as the sciatic nerve are involved, the method is contraindicated and amputation should be done.

3. Five cases are presented of the application of the radical-conservative method of dealing with superficial malignant tumors of the lower extremities.

*By Dr. Bruce Franz.

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A CONTROLLED SUCTION APPARATUS FOR GENERAL SURGICAL USE

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INTRODUCTION

CONTINUOUS suction of a predetermined degree is often mandatory in the postoperative care of surgical diseases. Common among such cases are those of thoracic empyema and intestinal fistulas. The principles involved in the surgical treatment of thoracic empyema have been reviewed by Carlson,[3] Connors,[4] Heuer,[12] and Bellis and Churney.[2] Each author has emphasized the importance of early and adequate thoracostomy, within the limitations derived from the investigations of Graham and his students,[6-9] and has stressed the value of suction. At about the third week after the onset of acute empyema, when mediastinal and diaphragmatic stabilization is usually adequate, open thoracotomy may be permitted without embarrassment of the vital capacity due to mediastinal shift. Re-expansion of the lung following thoracostomy is largely a function of the synechiae between the visceral and parietal pleurae, and may be accelerated by continuous suction applied to the thoracostomy tube. To this end, various devices for applying tidal irrigation and suction to the thoracostomy tube have been suggested by d'Abreau,[5] Hart,[10, 11] Wangensteen,[17] Lloyd,[14] Hochberg and Fiore,[13] Neville,[15] Touroff,[16] Weinberg and Sperling,[18] and Bellis.[1]

In the presence of bronchopleural fistula, constant suction applied to the thoracostomy tube is imperative lest the pus be aspirated into the bronchial tree. In the tedious management of intestinal fistulas, the nursing care parallels the nutritional problem in importance. It is well known that stomal narrowing in surgical ileostomy performed for chronic ulcerative colitis or in extraperitoneal intestinal resection performed for ischemic necrosis or for regional enteritis is enhanced by continuous suction applied to the abdominal surface. The ancillary effects of suction applied to traumatic intestinal fistulas are recognized similarly.

It is the purpose of this communication to describe a controlled constant suction apparatus similar to the one used at the University of Minnesota Hospitals.

APPARATUS

The tube coming from the patient is connected by a glass or metal Y tube to an additional 2 meters of pressure tubing attached to one of four pet cocks (Fig. 1, *PC*), each having an internal diameter of 8 mm. A common carryoff, 1.5 cm. in diameter, is abruptly turned through the metal screw cap of an ordinary 2,000 c.c. drain jar (*D*) for receiving the exudate or irrigant. A short length of intravenous tubing is attached to the third limb of the Y tube and clamped shut, being present for intermittent introduction of irrigant and for occasional measurement of the cavity capacity, if used for empyema. Suction is

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developed by a 1/8 h.p. motor at 1,725 r.p.m. (*M*), actuating a high vacuum pump (*VP*), capable of producing a vacuum of 0.0003 mm. of mercury. The rapid intermittent percussions are transmitted to a surge chamber (*SC*) of 1,000 c.c. capacity. The negative pressure (*NP*) is measured by an ordinary U type mercury manometer (*HgM*) and is transmitted to the drainage jar (*D*) by 4 mm. copper tubing. The joints between the metal screw cap and each of its penetrating tubes are soldered for airtightness. The negative pressure developed is maintained at a predetermined level by a mercury valve (*HgV*). This valve consists of an 8 by 1 inch test tube with accurately fitted two-hole rubber stopper, through one opening of which a glass tube, 3 or 4 mm. in diameter and open to the atmosphere at one end, passes through mercury to the bottom of the test tube. A short length of glass tubing passes through the other hole of the rubber stopper and is connected to the suction line between the surge chamber and the drainage jar by 4 mm. copper tubing.

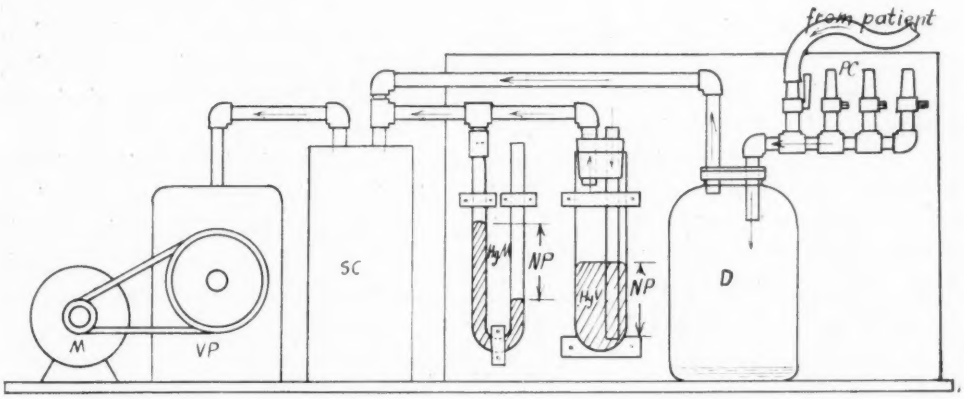

Fig. 1.—Mercury controlled suction apparatus. *D*, Drain; *HgM*, mercury manometer; *HgV*, mercury valve; *M*, motor; *NP*, negative pressure; *PC*, pet cocks; *SC*, surge chamber; *VP*, vacuum pump.

To increase the amount of suction, mercury is merely added through the open glass tube of the valve, the degree of negative pressure being equal to the length of the mercury column between the immersed tip of glass tubing and the meniscus. This length is always equal to the difference in height of the mercury columns in the two limbs of the manometer (*HgM*), since greater suction than this will be neutralized by air drawn through the open glass tubing. In operation, therefore, there is a shimmering or bubbling of the upper surface of the mercury in the valve due to the neutralizing air. The effect is to maintain the negative pressure at whatever the effective column of mercury is present in the valve.

The four pet cocks permit the suction to be available for four patients. Whatever cocks are not in use are turned off. With the arrangement described, the patient sleeps without being disturbed, and may sit in a bedside chair during the day, or stand at the bedside, without interfering with the operation of the suction.

After surgical drainage of an empyema pocket has been established by the insertion of a tube with multiple perforations into the most dependent and posterior portion of the cavity, an airtight seal is made at the point of entrance of the tube into the chest. This is done by pulling the tube through a rubber sponge saturated with yellow petrolatum or by surrounding the site with mechanic's waste similarly saturated. Multiple strips of adhesive tape, 6 or 8 cm. wide and 40 to 50 cm. long, further compress the sealing mechanism to insure airtightness. The degree of suction used in empyema depends upon the acuteness of the disease. An early empyema pocket may require 20 mm. of mercury negative pressure, whereas an older pocket with a less elastic visceral wall may necessitate as much as 100 mm. of mercury negative pressure. The degree of obliteration of the pocket may be measured by means of the Y tube. To do this, the motor is switched off and saline solution allowed to run into the empyema pocket by gravity through the extra limb of the Y tube until the liquid overflows. The tip of the Y tube limb is held at the level of the upper limit of the empyema pocket, and the saline solution is never admitted with extra pressure, such as with a syringe, for by so doing, the adhesions formed may be broken and the healing attained nullified. If the exudate is very thick, containing, as it often does, clumps, it may be necessary to dilute it every four or six hours by introduction, in a similar manner, of an irrigant.

The number of dressings required in the case of intestinal fistula is markedly reduced by taping the suction tube to the abdominal skin. Multiple perforations of the rubber tube, which is fixed in place to lie directly over the fistula, permit the drawing off of excretions which may contain particulate material of such dimensions which would occlude a single-hole tube. The apparatus has been found to be invaluable for this purpose.

COMMENT

Open or closed drainage, of course, must be deferred in empyema until the synpneumonic stage is over. In the metapneumonic or postpneumonic stage, suction is a definite therapeutic aid. In empyema thoracis, due to conditions other than pneumonia (such as fractured rib with laceration of the lung, gunshot or impalement wounds), the stability of the mediastinum and diaphragm is awaited before establishing thoracostomy. Additional information is given by the cellular content of the pus. However, the establishment of bronchopleural fistula must be considered a surgical emergency, whatever the degree of pleural thickening or density of the pus.

SUMMARY

The application of suction to the treatment of empyema thoracis and intestinal fistulas is discussed briefly, and an apparatus for this purpose incorporating a mercury valve for regulating the degree of negative pressure is described.

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SURGERY OF WAR WOUNDS OF THE ABDOMEN

A Review of One Hundred Consecutive Patients, Operated Upon by a Single Surgical Team, Working in Forward Areas in the European Theater of Operations

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IN WORLD WAR II, the mortality from abdominal wounds has been less than ever before. However, penetrating wounds of the abdomen still must be considered as among the most serious casualties of warfare.

The necessity of early operation in cases of penetrating abdominal wounds with visceral damage is now accepted so generally that controversy on this subject which went on before World War I has now completely ceased.

The incidence of abdominal wounds in the European Theater of Operations was 5.2 per cent, as compared with 43.6 per cent for the lower extremities, 27 per cent for the upper extremities, 4.4 per cent for the chest, and 12.5 per cent for the head and neck.

This series is presented to help evaluate the importance of some of the factors influencing the outcome in patients with abdominal injuries. It is a record of part of the experience of a single surgical team, operating in forward field hospitals of the Third Army, in its trek from Normandy through France, Germany, Austria, and Czechoslovakia. A surgical team consists of the surgeon, an assistant, an anesthetist, a nurse, and two enlisted men, traveling as a unit under orders of the army surgeon, to those field hospitals carrying the heaviest load.

Field hospital units were set up to support each division. The capacity of each unit was approximately 50 to 100 patients, and when filled to capacity it was leapfrogged by another similar group. Two surgical teams were assigned to each hospital, each team operating a twelve-hour shift. With the development of a heavy backlog of patients, it often became necessary to reinforce the operating personnel by the addition of more surgical teams.

Since it was necessary to remain mobile, all patients with abdominal injuries were evacuated as soon as they became transportable, which was usually seven to ten days following surgery. Such a period of postoperative stay in the hospital was recommended by the theater surgeon, and was usually of adequate duration.

During periods of stress, with the hospital under shell fire, it sometimes became necessary to evacuate patients earlier. In times of rapid advance, surgical teams were then sent forward to work in the clearing stations, leaving the hospital patients with so-called holding companies.

Treatment of abdominal injuries was definitive in character, and in most instances complete. The majority of patients arrived at the field hospital within from six to twenty-four hours following injury. The time of arrival was, of course, dependent upon many factors influencing the chain of evacuation. Fre-

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quently, field hospitals were located only three to four miles from the front. On several occasions (when the rivers Saar and Moselle were being crossed) because of blown-out bridges and the hazards of fire, it took some of the patients as long as forty-eight hours to arrive at the field hospital.

Preoperative Management.—It was imperative to improve the general condition of the patients before undertaking definitive surgery. Most of the wounded were admitted in a state of shock, and were immediately taken to a preoperative tent, where the extent of their injuries was evaluated and shock therapy instituted by special shock teams. Patients were prepared for surgery by transfusions of blood, plasma, and serum albumin when available. Blood, which was delivered daily by blood bank trucks, was of utmost value in preparing and fortifying the wounded for surgery. Treatment consisted of restoration of the circulatory blood volume by the rapid administration of blood and plasma, and of serum albumin. Blood was considered decidedly preferable, and the ratio was consistently kept to at least 50 per cent blood of the total of fluids administered. Dependable studies of blood volume losses made in forward hospitals indicate that soldiers seriously injured have averaged a loss of at least one-third of their total blood volume. It has been stated by Cutler that a blood pressure of 85 mm. of mercury systolic usually indicates such loss of one-third of the blood volume.

The amount of fluid given varied in each case, depending upon response of the individual patient. A level of systolic blood pressure of at least 100 mm. of mercury was regarded as desirable prior to operation. An improvement in pulse volume, indicating an increased cardiac output, was considered almost as important as a rise in blood pressure. Not uncommonly, 3 to 6 L. of fluid had to be administered before the patient could be taken to the x-ray and surgery tent. Very few patients were admitted to the operating tent without having had at least 500 c.c. of blood administered.

The infusions were given rapidly, and the response to adequate replacement of blood volume loss was often very gratifying. Two or three veins were frequently chosen for simultaneous administration of fluids. The external jugular vein was often utilized by the anesthetist who administered the fluids in the operating room. The femoral vein was occasionally used in emergencies, no other veins being available.

Blood was practically always on hand, and was usually supplied in the form of Alsever's solution (500 c.c. of blood and 500 c.c. glucose and electrolyte). It was delivered to the field hospital ten days after it had been drawn in New York or Boston. Cutler, in a recent report, stated that from May 22, 1944, to May 31, 1945, 385,291 pints of blood were used in the European Theater of Operations; 194,712 pints were flown over from the United States.

Serum albumin, when available, was very helpful and useful in combination with blood. The response to 100 c.c. of serum albumin administered rapidly to a pulseless patient in deep shock was often dramatic.

Shock was further treated by the elevation of the foot of the litter in a modified Trendelenburg position. Oxygen was administered in all cases of se-

vere shock, especially to those patients with associated chest injuries. Large doses of coramine, 10 to 12 c.c., seemed to be of some value in a few cases, when given together with replacement therapy. Patients were not moved, often coming to the operating tent on the same litter on which they were admitted. The patients were operated upon on this litter, and moved only to a cot in the postoperative ward.

A few hours' delay to prepare the patient for operation was found to be justified. Failure of the patient to respond to therapy within two hours, or relapsing shock, usually indicated continuing internal hemorrhage. This necessitated immediate exploration in spite of the risk involved in the presence of shock. Two deaths on the operating table occurred in this group of cases.

Delay between admission and operation was usually not more than two to four hours. Occasional further delay was due to large numbers of casualties admitted within a short period.

Concomitant with the improvement in the general condition of the patient, a careful appraisal of the abdominal injury was made. Wounds of entry and exit were examined. The possibility of missiles entering the abdomen from above through the diaphragm or from below by way of the buttocks, back, or thighs was considered.

As soon as the patient's condition permitted, x-ray examination of the chest and abdomen was made. The chest was x-rayed in every case of abdominal injury and the abdomen in every case of chest injury in order to determine the location of the missiles, to decide whether penetration of the peritoneal cavity had taken place, and to help in planning the operative procedure. Urine examination was done routinely in all cases; whenever the patient was unable to void, catheterization was carried out and in case of hematuria an indwelling catheter was left in place. Hematuria due to kidney or bladder involvement was quite common. Rectal and proctoscopic examinations occasionally revealed previously undiagnosed injuries of the lower bowel.

Every patient admitted for intra-abdominal injury had the stomach emptied by gastric suction before he was taken to the surgical tent. Preoperative gastric suction prevented acute gastric dilatation and diminished the likelihood of aspiration of vomitus, with its dire consequences. At the completion of surgery the indwelling gastric catheter could often be threaded into the duodenum, assuring a smoother convalescence, especially if suture or resection of the small bowel had been performed. The Miller-Abbott tube was successfully used in a few cases of small bowel obstruction which developed during the first postoperative week.

In spite of the fact that the front line was only a very few miles away, the time lag between injury and admission to the hospital was often quite considerable. The average interval for seventy-two cases of which such records were kept was 15.6 hours. This time lag between injury and surgical care has long been considered a major factor affecting the mortality rate. However, that it is not the only decisive element is illustrated by the fact that for a period of about one week (the crossing of the river Saar by the 90th Division) casualties could not be evacuated across the river except at

night, because of hazardous enemy fire: and yet, forty-five patients with abdominal and chest injuries were operated upon by two surgical teams, without a single surgical death. The only death in this group occurred in the preoperative tent, and was due to irreversible shock resulting from bilateral traumatic amputation. Some of these patients were admitted as late as sixty hours after injury. It is likely that those most seriously wounded must have died before reaching the field hospital.

Of the fourteen patients who died, the average lag from injury to time of operation was fourteen hours. Twelve of these were in profound shock upon admission. It is interesting to note that the time lag for all cases in which it was recorded (seventy-two) averaged 15.6 hours, indicating again that the time factor is probably not as important as heretofore assumed.

The extent of injury and the degree and persistence of shock are of such primary importance that the delay of surgical treatment can be regarded as relatively less critical. The danger of infection which is so closely related to the time interval before operation has been considerably reduced as a result of chemotherapy.

Anesthesia.—Ether was the anesthetic agent of choice. It was administered preferably through an endotracheal tube. The tube affords better control of the respiratory exchange and depth of anesthesia. Opportunity for aspiration of foreign material was thus lessened, and the prevention of postoperative pulmonary complications through easy therapeutic aspiration of mucus and secretions in the bronchial tree was considered important.

The addition of bilateral intercostal block with novocain was found to be helpful in securing relaxation of the abdominal wall and facilitating the operation, especially in those poor-risk patients in whom deep anesthesia was likely to result in a further drop of the blood pressure. Curare was not available, and would probably have been contraindicated under the prevailing circumstances.

Missiles Producing the Wounds.—The type of missile and the nature of the wound produced have apparently little effect upon the rate of mortality. It is rather the extent of the injury and amount of visceral damage, reflected by shock and hemorrhage, which are the decisive factors. It might be said that abdominal wounds due to mortar fire were the worst seen, in that they were multiple. The through-and-through injuries made by rifle and machine-gun bullets were much less severe.

Incision.—The location of the wound and the site of the missile and foreign bodies, as indicated by the x-ray examination which helped visualize the course of the projectile, were important factors in planning the incision. For through-and-through injuries in either the right or left upper quadrants, transverse subcostal incisions were utilized as often as possible. Long pararectus incisions were reserved for patients with multiple injuries. Colostomy, when indicated, was usually done through a smaller stab wound, lateral to the incision. Drainage of the peritoneal cavity was deemed necessary only infrequently. The retroperitoneal spaces involved, however, were drained almost routinely. Closure of

the incisions was accomplished in layers with interrupted silk, with the addition of heavy retention sutures, spaced about one inch apart to include all layers. The skin was not closed in wounds with marked contamination. Wound infections were not encountered during the seven- to ten-day stay of the patients in the field hospital.

Extent of Visceral Injury.—The mortality was directly proportional to the extent of visceral injury. There were 14 deaths in this series of 100 cases, and each of these patients had suffered multiple injuries. The organ most frequently injured among the fatal cases was the colon. Very few instances occurred in which only a single viscus was affected, and no patient in that group died. In the following discussion of abdominal war wounds it should be noted that only multiple injuries affecting several viscera caused the fatal outcome of cases. Each fatal case, therefore, appears in the following under as many headings as viscera were involved.

TABLE I. ORGANS INVOLVED IN 100 CASES (WITH DEATHS LISTED ACCORDING TO ORGANS)

ORGAN	NUMBER OF CASES	NUMBER OF DEATHS
Stomach	7	1
Duodenum	3	1
Small intestine	28	6
Colon	26	8
Rectum	3	1
Bladder	6	0
Gall bladder	1	0
Liver	30	3
Pancreas	1	0
Spleen	9	1
Kidney	19	3
Retroperitoneal hematoma	29	5
Thoracoabdominal	25	3
Negative exploration	6	0
Evisceration	8	2

Stomach.—Seven patients were admitted with perforation of the stomach. In each of these, other visceral damage was present, consisting most frequently of liver injury. One death occurred, the wound of entrance in this case being through the right axilla; there was also laceration of the right lung and diaphragm, and of the liver, stomach, and colon. The sucking wound of the right side of the chest was closed, as were lacerations of the stomach at laparotomy; bleeding from the liver was controlled, and the ruptured colon exteriorized. Death occurred on the third postoperative day, from atelectasis and bronchopneumonia.

Duodenum.—There were three cases of injury to the duodenum. The stomach and pancreas were also involved in one; the retroperitoneal portion of the duodenum, liver, and stomach in the second. These two patients recovered. A third one, a 65-year-old French civilian woman, had two perforations of the first portion of the duodenum, and lacerations of the liver and the left kidney. She died four hours after operation.

Small Intestine.—The small bowel was injured in twenty-eight cases. Multiple perforations were the rule, and as many as fifteen were sutured in a single individual.

There were six deaths in cases involving injury to the small gut. The mortality in the cases of resection of small bowel was approximately the same as in those in which closure of multiple perforations was done, in spite of the fact that resection was resorted to only when the extensive injury to the bowel precluded simple closure of the perforations. There were nine resections of the small bowel, with two deaths. In both of these fatal cases the patients were admitted with evisceration; in one there was marked involvement of the terminal ileum and practically complete destruction of cecum and ascending colon. Resection of the terminal ileum and right side of the colon had to be done with ileocolostomy. The defect in the abdominal wall was so great that closure could be accomplished only by substituting a large petrolatum pack for abdominal wall. The patient died two days later of pulmonary complications. The second death following resection of small gut occurred in a patient with extensive injury to the colon as well as to the right arm, with destruction of the brachial artery. The arm had to be amputated. The patient died within twelve hours of irreversible shock.

There were nineteen cases of injuries to the small bowel, in which simple closure of multiple perforations was done. Four deaths occurred. One patient had compound comminuted fracture of the femur, evisceration, and six perforations of the small gut. The second had laceration of the colon, small bowel, and injury to the spinal cord. The third was admitted with fractured femur, ruptured colon, and ten perforations of the small gut. The fourth had ten perforations of the ileum as well as injury to the region of the left ureter.

Colon.—In twenty-six cases, injury to the colon was noted. Eight deaths occurred in this group. All of these were associated with severe injuries to other viscera, as small bowel or kidney, or with fractured femur, evisceration, and severe shock. The small bowel plus the colon were injured in four of these fatal cases; kidney plus colon in two cases; liver, stomach, and colon in one case; severe retroperitoneal hematoma and colon in one case. Colostomy was always carried out for injury of the colon, and in cases of injury to the rectosigmoid, the perforations were closed and colostomy performed on the sigmoid for complete diversion of the fecal stream. Colostomy was done routinely for all injuries to the rectum. Massive inundation of the peritoneal cavity with the fluid feces, through multiple perforations of the lower small bowel and colon, especially if associated with massive retroperitoneal hematoma with kidney injury, seems to be productive of severe unremitting shock. This was true of each one of the eight colon cases in which the patient died. The role of massive bacterial spillage in establishing deep shock has recently been emphasized by Jarvis and associates.

TABLE II. MORTALITY AS AFFECTED BY ASSOCIATED INJURY OF THE COLON

ASSOCIATED INJURY	NUMBER OF CASES	NUMBER OF DEATHS	PER CENT MORTALITY
Small bowel injury without colon injury	17	2	11.7
Colon or rectosigmoid injury without small bowel injury	15	4	26.6
Colon plus small bowel injury	11	4	36.3

Rectum.—There were three cases of injury to the rectum. The wounds were débrided. Perforations of the rectosigmoid were closed and abdominal colostomy was carried out. The coccyx was excised for adequate drainage of the retroperitoneal space. No fatalities occurred in this group.

Bladder.—In six cases the urinary bladder was perforated. There were no deaths. Four of these patients suffered involvement of the small bowel or colon. Once there was associated compound comminuted fracture of the femur. In only one case was injury to the bladder noted without any concomitant visceral damage.

Liver.—Wounds of the liver were encountered in thirty cases. It was the organ most frequently injured. There were three deaths, one from laceration through the porta hepatis, involving severe injury to the liver. Death was due to bile peritonitis. The second was the 65-year-old French civilian woman previously mentioned, and involved laceration of the duodenum, left kidney, and liver. The third presented a combination of injuries to the chest, lung, diaphragm, liver, stomach, and colon.

Drainage of the subhepatic and subdiaphragmatic space was carried out routinely when laceration of the liver was present or when laceration of the liver was found during repair of the right diaphragm. No attempt was made to remove foreign bodies which were deeply embedded in hepatic substance. Control of bleeding from liver injury seldom presented serious difficulty. Packing with gauze usually proved sufficient, and suture was performed only infrequently. In one instance, perforations of the gall bladder were closed with subsequent uneventful recovery.

Only one case of direct injury to the pancreas was recorded. There was in that case associated injury to stomach and duodenum. The patient recovered.

Spleen.—Severe hemorrhage from rupture of the spleen necessitated splenectomy in five cases. In four other instances of bruises or minor lacerations of the spleen, hemorrhage had ceased and the spleen was not removed. Conservatism in this group seemed justified as no subsequent deaths occurred, and complications due to delayed hemorrhage did not take place. The surgical approach was usually through a left subcostal incision. Transthoracic splenectomy was carried out three times when a left thoracoabdominal wound was present. There was one death in this group. It was a case of left thoracoabdominal injury, a large sucking wound of the left chest with evisceration of omentum, laceration of diaphragm, and ruptured spleen. Profound shock persisted, from which the patient could not be rallied in spite of massive transfusions. As it was obvious that without immediate surgery the patient would die, exploration and splenectomy were done. Death, however, occurred on the operating table.

Kidney.—The presence of renal injury was usually indicated by the location of the missile, which was established by x-ray examination and by the presence of gross hematuria. There were nineteen cases in which injury to the kidney was reported, and three deaths. All three patients had suffered associated severe intra-abdominal injuries involving the colon; one had also suffered rupture of the diaphragm and spinal cord injury. The combination of

kidney and colon injury always seems to be a serious one. Conservatism was the rule, and nephrectomy was carried out only twice in patients in whom exploration revealed the kidney to be ruptured or hopelessly injured. In all cases hematuria disappeared within a few days. An indwelling catheter was left in the bladder until the urine was clear grossly. In no instance was it regretted that nephrectomy had not been performed. The wounds were débrided and liberal drainage was provided for. In conservatively treated patients significant postoperative secondary renal hemorrhage or severe infection did not occur while the patient remained in the field hospital.

Thoracoabdominal Wounds.—In twenty-five cases, injury of the chest was associated with abdominal damage. The abdominal involvement was caused either by penetration through the diaphragm or by a separate injury. There were three deaths. One was a case previously mentioned, in which splenectomy was carried out through the chest; the second involved a sucking wound of the right side of the chest with injury to the diaphragm, liver, stomach, and colon; in the third case, the patient had a sucking wound in the left side of the chest, associated injury to the left diaphragm, and had also been wounded in the left kidney and suffered severe retroperitoneal hemorrhage, with complete paraplegia due to spinal cord injury.

The presence of abdominal rigidity, associated with penetrating wounds of the chest and especially with multiple fractured ribs, was noted quite frequently. Usually it was unilateral, and unless examination of the path of the missile revealed intra-abdominal penetration, laparotomy was not done. Acute dilatation of the stomach was a frequent complication of thoracic injury. Decompression of the stomach in these cases was considered essential to improve respiratory exchange.

In the combined chest and abdominal injuries, it was preferred to perform the chest surgery first. It was considered important to stabilize the respiratory exchange, reduce shock, and give the patient the maximum benefit of relief from anoxia, before proceeding with the abdominal exploration. This involved such procedures as relief of tension pneumothorax, aspiration of hemothorax, and closure of sucking wounds.

The common intrathoracic procedures were aspiration of hemothorax, removal of foreign bodies and embedded fragments from the lung, and suture of lacerated lung and diaphragm. In large penetrating and sucking wounds the approach to the upper abdomen through the diaphragm was considered to be most appropriate. Suture of the diaphragm was relatively easy, and exploration of the upper abdomen, splenectomy, etc., was readily accomplished in this manner.

Negative Exploration.—In six cases the abdomen was explored with negative findings. No injuries to the intraperitoneal organs were found, and no deaths occurred. These patients, of course, would have fared better without laparotomy, but it was preferable to have erred on the side of intervention rather than to have omitted exploration. In one case, exploration at first also seemed to be negative, until careful search revealed a small perforation at the apex of

the splenic flexure of the colon. In many cases, following débridement of the tract of the missile with its recovery (extraperitoneally) in the abdominal wall, laparotomy was not performed.

Evisceration.—Evisceration was present in eight cases; two of these patients died. In one, the defect of the abdominal wall was at least 8 by 10 cm. in size. Multiple injuries to the large and small bowel were also present. Resection of the right side of the colon and ileocolostomy was considered necessary; reconstruction of the abdominal wall was carried out over a petrolatum pack. The patient died three days later of pulmonary complications. The second soldier admitted with evisceration died of irreversible shock due to severe injuries to the colon, jejunum, and abdominal wall as well as compound fracture of the forearm, which necessitated amputation.

Chemotherapy.—Chemotherapy has played a significant role in the low mortality of this series and is responsible for the absence of severe peritoneal infection following abdominal injury. At completion of laparotomy it was customary to leave 100,000 units of penicillin in the peritoneal cavity, following which 40,000 units were administered every four hours intramuscularly. Intramuscular administration of penicillin was started as soon as the patient was admitted and continued as long as he remained at the field hospital. In thoracoabdominal wounds 100,000 units of penicillin in saline solution were instilled into the chest before closure. The sulfonamide drugs were not used locally, intraperitoneally or intrapleurally. Sodium sulfadiazine intravenously, 3 Gm., was administered as soon as the patient was out of shock. Postoperatively, 6 Gm. daily were administered in the intravenous solutions. No case of renal blockage from sulfadiazine crystals was observed, although cystoscopy was performed in cases of anuria to rule out this complication. Every four hours, 1 Gm. sulfadiazine with soda was given by mouth as soon as alimentation was begun. In the course of four days this dosage was reduced to half, and subsequently discontinued, in accordance with the progress of the patient. Very few drug reactions were seen at the field hospitals.

Postoperative Care.—Careful attention to the details of postoperative care was considered of utmost importance. Blood volume was supported with blood and plasma, after return to the ward tent. Gastric suction was maintained for several days, until the re-establishment of normal peristalsis, as evidenced by passage of gas per rectum. Plasma was given daily in amounts of 500 to 1,000 c.c., in an effort to maintain nitrogen balance. Parenteral fluids, glucose in water and saline solution to a total of 3,500 c.c., were given during four to five days, until diet was tolerated by mouth.

If distention appeared or obstruction seemed to be developing in spite of the Wangensteen suction it was removed and replaced with a Miller-Abbott tube which in most cases was readily passed into the upper reaches of the small bowel, using mercury to weight the balloon. In only two cases did the procedure fail to decompress the bowel. One of these patients was operated upon with successful outcome, for release of adhesive obstruction, at a rear hospital to which the patient had been evacuated. The second died of peritonitis and obstruction at multiple adhesive points.

Particular attention was paid to the possible development of pulmonary complications. Cough and deep breathing were encouraged, and the patients were turned frequently. Occasional bronchoscopic aspiration in the early stages of atelectasis was necessary. Intercostal block with novocain, especially in the chest cases, helped patients to raise sputum without pain. Postoperative atelectasis and pneumonia were responsible for four deaths. Injuries which immobilized the patients, such as associated fractured femur or spinal cord injury with ensuing paralysis, were major factors contributing to pulmonary complications in one-half of these cases.

Use of Morphine.—The abuse of morphine as a pain-relieving agent was encountered relatively often. Wounded soldiers were frequently given half-grain doses subcutaneously, as soon as they received first medical aid. A similar dose was often administered at battalion aid, collecting company, or clearing station. During this repeated procedure the patient was in shock, and the circulation was unable to pick up the subcutaneously administered morphine. Later, after adequate treatment of shock and increase in blood pressure, the accumulated morphine was suddenly absorbed and the patient developed all the signs of morphinism with its anoxia, Cheyne-Stokes respiration, etc. Oxygen and coramine were found to be of value in such cases. In a few instances, precious hours were lost before the patient could be operated upon as a consequence of too much morphine. Intravenous administration of morphine is much to be preferred, and the drug should be given in this manner whenever possible. The administration of an overdosage of morphine should be avoided in patients already anoxic from shock, as restlessness from cerebral anoxia is thereby aggravated.

Analysis of Deaths.—The mortality in this series was 14 per cent. Of the fourteen deaths, six were due to irreversible shock. Two patients died on the table, and four others within forty-eight to seventy-two hours, of progressive irreversible shock. One death followed a severe bile peritonitis. Three deaths resulted from diffuse peritonitis. These patients had suffered multiple perforations of small bowel and colon. Pulmonary complications were responsible for four deaths.

TABLE III. CAUSES OF DEATH IN 100 CASES

CAUSE OF DEATH	NUMBER OF DEATHS
Irreversible shock	6
Bile peritonitis	1
Diffuse peritonitis	3
Pulmonary complications	4
Total	14

Peritonitis.—In this entire series there was no instance of diffuse suppurative peritonitis in the true sense of the word. Among the patients examined at post-mortem, none were seen with the abdomen distended by pus, as was often the case at autopsy following intestinal perforation and operation, before the era of chemotherapy. The cases of peritonitis observed were of the fibrinoplastic type producing dense adhesions, which resulted in numerous points

of mechanical obstruction. Whenever purulent exudate was found, it was observed to be well localized. Such collections were occasionally seen in the subphrenic area.

DISCUSSION

The experience with penetrating wounds of the abdomen obtained by a single surgical team in forward field hospitals is hereby presented. In 100 consecutive cases of abdominal injury, 14 deaths are reported, a mortality of 14 per cent. Excluding injury to solid organs there were 11 deaths in 74 cases of injuries to multiple hollow viscera. This mortality is much lower than that of World War I, and compares favorably with recent publications from World

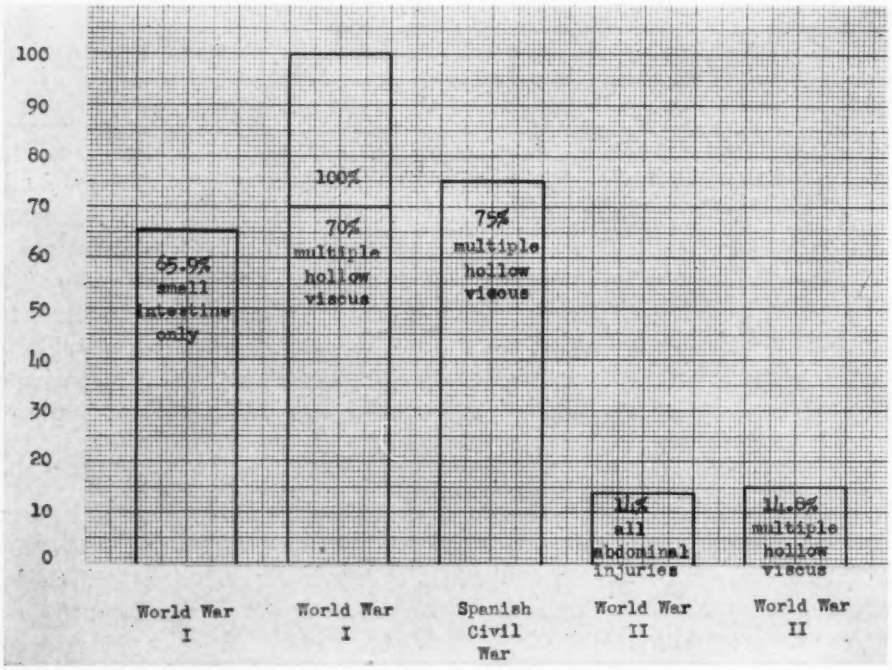

Fig. 1.—Comparison of mortality in different wars.

War II. It is realized, of course, that subsequent deaths may have occurred following evacuation of the patients to the zone of the interior. Personal follow-up could not be carried out in every case, although we have had communication from about one-half the number of patients after their evacuation to the rear.

The marked improvement in the mortality rate, as compared with World War I, may be illustrated by the following figures quoted by Bailey: A series of 255 cases from World War I, collected by Sir Cuthbert Wallace, in which the injuries reported upon were restricted to the small intestine, showed a mortality of 65.9 per cent. When perforation of the small bowel was accompanied by wounds of other hollow viscera, the mortality figure varied between 70 and 100 per cent.

In the recent Spanish Civil War, which began in 1936, a series of 240 cases of lesions of gastrointestinal involvement alone or conjointly with other visceral wounds was reported upon. Only 25 per cent of the patients recovered.

Similar recent series from World War II, as published by Imes, Bradford and associates, and Jarvis and associates revealed an over-all mortality of approximately 20 per cent.

It is difficult to ascribe the lowering of mortality to any one specific factor—penicillin, sulfadiazine, blood, plasma, plus above all watchful postoperative treatment and alertness for possible complications. The careful treatment of shock is probably the most important single item. Adequate decompression of the bowel by gastric suction syphonage before, during, and after surgery should be mentioned as having played an important role.

Conversation with German medical personnel in captured enemy field hospitals elicited the following information: Their best mortality claim was 30 to 50 per cent. Gastric suction was not utilized by the Germans. While plasma was available, blood was not, and direct transfusions were the rule. The Germans had sulfonamide preparations comparable to ours, but no penicillin.

Much credit is due to the Medical Corps of the United States Army for its wonderful organizational and supply system, as well as to the enlisted men and nurses, who assisted in Army Field Hospitals. The excellent service rendered by the personnel responsible for the successful administration of the blood banks cannot be praised too highly.

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Recent Advances in Surgery

Conducted by Alfred Blalock, M.D.

THE IMPORTANCE OF NONSURGICAL MEASURES IN THE TREATMENT OF INTESTINAL OBSTRUCTION

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IN SPITE of the fact that the local and systemic effects of acute intestinal obstruction have been well known for many years, the morbidity and mortality rates in many hospitals throughout the country are still too high. This means that there are many physicians, and surgeons as well, who either do not understand both the anatomic and the physiologic changes that take place in intestinal obstruction, or do not properly combine the nonsurgical forms of treatment with prompt surgical intervention. Although this paper is not concerned with the surgical aspect of the treatment of intestinal obstruction, I should like to make it clear at the outset that if a diagnosis of mechanical obstruction can be made, surgical intervention is without doubt the proper treatment. The nonsurgical measures which will be discussed here are the necessary adjuvants both before and after operation, but are not to be considered as primary forms of treatment in themselves.

Before we consider the various nonsurgical forms of treatment and their rationale, we should have a pretty clear picture of the disturbed physiology of both the involved intestine and the patient as a whole. When obstruction of the bowel develops from some cause, there follows a sequence of events with, first, gradual ascending distention of the bowel above the constriction, followed by alteration in the absorptive and secretory functions, impairment of circulation, and finally gangrene if the obstruction is not relieved. Vomiting usually begins early and continues with the resultant loss of fluids and electrolytes, and dehydration rapidly develops. Also as the blood supply of the bowel becomes impaired by distention or actual strangulation, as in volvulus or strangulated hernia, fluid pours out into the peritoneal cavity, and there is loss of plasma as well. Unless relief is afforded the process continues and the patient lapses into a state of shock followed by death. It can be seen, therefore, that if a patient is suffering from a mechanical obstruction of the small bowel caused perhaps by a single band of adhesions from an old operative wound, even though proper surgical measures may be instituted the patient may nevertheless die if adequate steps are not carried out to combat the loss of electrolytes, the hemoconcentration, and the low plasma proteins that have resulted from the obstruction. It may be helpful to enumerate some of the lifesaving measures that should be begun in every case immediately after a presumptive diagnosis of mechanical obstruction has been made, before operation can be considered.

As a result of vomiting and the outpouring of fluids into the peritoneal cavity, three definite changes take place. The first change is a fall in the blood

chlorides; second, there is a rise in the nonprotein nitrogen; third, there is an increase in the carbon dioxide content of the blood. The fall in the blood chloride was first described by MacCallum and his associates[1] in 1920; the rise in the nonprotein nitrogen was described by Tileston and Comfort[2] in 1924. The increase in the carbon dioxide content of the blood had been previously reported by McCann[3] in 1918. These changes are all well understood now, but it is interesting to note that in 1912, before these studies were carried out, Hartwell and Houget[4] made the observation that in acute intestinal obstruction, life could be prolonged by the injection of saline solution. They attributed this fact chiefly to the relief of dehydration, rather than to the introduction of chlorides. In 1927 White and Bridge[5] carried out some experiments on dogs in which they completely obstructed the duodenum and then studied not only the changes in blood chlorides but also the chloride content of various tissues. They came to three definite conclusions:

"1. The fall of chloride in the tissues parallels that in the blood.

"2. The loss of chloride from the blood and tissues corresponds with the total amount lost through all channels of elimination, and

"3. Only the administration of both chloride and water can prevent a fatal alteration in the chemistry of the blood and tissues."

They also agreed with other investigators who have shown that neither water alone nor isotonic glucose solution is sufficient to prevent a fatal alteration in body chemistry in intestinal obstruction.

Even though these facts are incontrovertible, many times they have not been applied intelligently in the treatment of the altered electrolyte metabolism of intestinal obstruction. This has been an important reason for the continued high mortality figures in intestinal obstruction. The work of Coller and Maddock[6] has probably done more than anything else in recent years to call attention to the importance of electrolytes not only in cases of obstruction but also in many other conditions, before and after operation. It is still true, however, that too often fluids containing electrolytes are given in a haphazard manner. Many times 500 or 1,000 c.c. of glucose in normal salt solution or in distilled water are given to a patient as a matter of routine instead of analyzing his specific needs by careful evaluation of the clinical and laboratory data available. Therefore, in a patient with evidence of intestinal obstruction, the length of time since the onset of symptoms, the amount of vomiting, and the level of the obstruction, whether high or low, are all factors that will determine the electrolyte needs of the patient. The laboratory determinations of the blood chlorides and nonprotein nitrogen as well as the plasma proteins are also of importance and are points to be considered in determining what replacement of crystalloids will be necessary not only to get the patient into the best condition for operation, but often to save his life. It must be realized, however, as pointed out by Coller and his associates,[7] that there is no rule of thumb whereby it can be determined how many grams of electrolytes each individual patient may need. In the summary and conclusions of this excellent article, in pointing out the fact that sodium chloride can be toxic if given in too large quantities under certain conditions, Coller says, "It is recommended that the correction of uncompensated

extra-cellular fluid deficiency states be made upon the basis of the physiologic response to test doses of the appropriate salt solution rather than upon the basis of the plasma chloride, the CO_2 combining power, the N.P.N., the plasma protein, or the hemoglobin levels.''

Besides the loss of electrolytes in all cases of obstruction, there is the concomitant loss of fluids with resultant dehydration and hemoconcentration. Even though vomiting may not have been a prominent symptom, as is often the case in low obstructions, as the bowel gradually distends above the level of the obstruction there is disturbance in the secretory and absorptive mechanism. This results in the loss of large quantities of fluid in the dilated loops. Also, in cases where there is strangulation of a portion of the bowel there will be a considerable outpouring of fluid into the peritoneal cavity. As Blalock[8] has pointed out, the initial loss of water is usually at the expense of the interstitial fluid of the body and only secondarily from the blood plasma. The intracellular fluid is usually not affected by moderate loss of water. However, when the resorptive function of the bowel is upset and when we realize that the normal amount of gastrointestinal secretions in twenty-four hours exceeds by several times the quantity of fluid taken by mouth, it can be seen that rapid dehydration may result. It is, therefore, necessary to give parenteral fluid preoperatively, during the operation, and after operation as well. In trying to determine the amount of fluids there is no formula that can be applied. From the practical standpoint both of electrolyte and the fluid balance can be restored safely and effectively by beginning with the administration of 1,000 c.c. of 5 per cent glucose in normal saline solution and following this with 1,000 c.c. of 5 per cent glucose in distilled water. Then, depending upon the response of the pulse rate, the blood pressure, and the general condition of the patient, the decision as to further fluid and electrolyte requirements should be made.

As stated previously, in all cases of obstruction there is not only the loss of fluid and electrolytes but also plasma proteins to a greater or lesser degree. When the obstruction has been of short duration, the loss of protein is not great and its significance as far as life and death are concerned does not amount to very much. Under these circumstances the adequate replacement of water and crystalloids will prepare the patient properly for operation and will also suffice after operation until he can take protein by mouth. This will be true in most cases of obstruction that are not of long standing, or in which there is no malignant neoplasm as the primary cause of the obstruction. In the latter case, however, the loss of protein can be considerable, and although it may not have been recognized, the state of nutrition of the patient probably had been below normal for some time. There is no doubt about the fact that in many cases the deleterious effect of an existing hypoproteinemia has not been fully recognized. Ravdin[9] was correct when he indicated that too much emphasis, if that is possible, has been placed on the water and salt requirements of the surgical patient and too little emphasis on the mechanisms involved in keeping fluid in the blood vessels. In other words, we should be concerned about the existence of hypoproteinemia. Until recently there were only two substances that could be given intravenously that would help to restore lost protein, and these were whole blood and plasma.

With the establishment of blood banks in many hospitals, whole blood has been made readily available, and it can adequately supply the necessary protein, but repeated transfusions are necessary. Plasma as a source of protein for intravenous administration can maintain nitrogen balance as shown experimentally by Holman, Mahoney, and Whipple.[10] It has certain drawbacks as a source of nitrogenous nourishment, however. It would be necessary to give 500 c.c. of plasma in each twenty-four hour period in order to supply 35 Gm. of serum protein. This amount is at the low level of normal needs for an average adult but it is only the one protein, serum protein. The work, first, of Elman[11] and later of others, however, has shown that protein in the form of all the necessary amino acids can be given along with crystalloids in sufficient quantities to correct the condition of hypoproteinemia and a positive nitrogen balance can be created. It is now possible with amigen and other similar preparations that are available to cover not only the protein needs of the patient but even to make up deficits within a reasonable time. There is reliable evidence that glucose is necessary for the complete utilization of protein when given intravenously in the form of amino acids. Therefore, if the patient is an adult of average weight with a moderate protein deficit, to whom we give 3 L. of fluid of which 1 L. is amigen solution containing 5 per cent each of amigen and glucose, the other 2 L. being 5 per cent glucose, the patient will receive 3,000 c.c. of water, 5 Gm. of electrolyte, 150 Gm. of glucose, and 50 Gm. of protein. If further increase of electrolytes is needed, 1 or 2 L. of the 5 per cent glucose solution can be given in normal saline solution. These amounts can be given very easily by what Elman[11] likes to call intravenous alimentation in any twenty-four hour period; in this way the requirements of the average adult will be met for water, electrolytes, calories, and protein.

Some mention should be made at this time of vitamins. There is no doubt that vitamins have been advertised for commercial purposes far out of proportion to the real need for them. In the nonsurgical treatment of most cases of intestinal obstruction, vitamin therapy is not necessary because of the short duration of the symptoms both before and after operation. There are some patients, however, with a neoplasm of long-standing chronic infection as the primary cause of obstruction, in whom a true vitamin deficiency develops. If this is the case there are active vitamin preparations now available that can be given parenterally when needed.

It can be said without fear of contradiction that one of the most valuable adjuvants that we have at our disposal in the nonsurgical treatment of intestinal obstruction, no matter what the etiology, is the Levine tube. Its value has been appreciated for many years, but Ward[12] was the first to apply continuous suction to the tube in cases of intestinal obstruction. Wangensteen and Paine,[13] however, are responsible not only for realizing the possibilities of duodenal suction in the treatment of all forms of intestinal obstruction but also for presenting a practical method that has undoubtedly saved many lives. There is little doubt that there is a certain percentage of cases of obstruction which can be relieved permanently by duodenal suction, but it is important to remember what Wangensteen and his associates[14] reported: "The relative indications for

the employment of suction are so many that it would be well to reiterate a warning which has been uttered on other occasions, namely, the practice of employing suction as a test procedure to indicate whether operation will be necessary leads only to deferment of appropriate treatment. Neglect of this admonition is the most mischievous error into which one may fall in the application of suction to patients with intestinal obstruction.'' Too often when we have a form of treatment that at times gives dramatic results we do not realize its shortcomings as well as its advantages, and hence we feel a false sense of security. Therefore, if the duodenal tube is used early with the knowledge that it is an adjuvant in the diagnosis and treatment, and if operation is not delayed when all indications point toward its necessity, suction decompression of the stomach and upper intestinal tract will prove one of the most valuable aids that we have.

There are certain points in the proper use of a duodenal tube for suction decompression that are important. In the first place it is always wise to explain to the patient what is going to be done and the reasons for passing the tube, and also that it may be necessary to leave the tube in place for three to six days, depending upon the course of events. With the patient in high Fowler's position, the duodenal tube is passed through the nose until it reaches the stomach. It is always wise to allow the escape of as much fluid and gas as will come before suction is applied. After a short time a very moderate degree of suction is applied to discover whether there is further return of gas or of the contents of the upper intestinal tract. If the process of decompression continues it can be aided by alternately applying gentle suction and cutting it off. If, however, the stomach is emptied and there is no further recovery of fluid or gas, it is advisable to cut off the suction, place the patient on his right side, and then advance the tube about one inch every five or ten minutes. In this way it is possible in perhaps 50 per cent of the cases to get the end of the tube through the pylorus and so decompress the upper small bowel. If it is established that the tube is in the duodenum, either by the recovery of bile or by the decompression of distended loops of small bowel, it is wise to keep a moderate degree of suction on the tube.

In a majority of cases of intestinal obstruction the question arises as to how long suction drainage should be applied before surgery is resorted to. This question cannot be answered in a dogmatic way because the limitations in the diagnosis of acute abdominal disorders are too often plain to both the physician and the surgeon. However, again as Wangensteen and co-workers[14] have pointed out, when the significance of intestinal colic, the presence or absence of signs of peritoneal irritation, and the character of the aspirated gastric contents, together with the flat x-ray film of the abdomen are fully evaluated, it is usually possible to arrive at certain reasonably accurate conclusions. These are, first, whether obstruction is present, and, if so, at what level. Second, it may be possible to determine whether there is strangulation of bowel, and, finally, whether the obstruction is complete or incomplete. On the bases of these conclusions it should be possible to determine whether it would be safe to temporize for a while even though the exact nature of the pathologic process remains conjectural. One rule, however, can be fairly definitely laid down; namely, if col-

icky pains continue after the decompression of the stomach and there has been time for even partial restoration of the fluid and electrolyte balance, immediate surgical exploration is mandatory. The two most difficult types of cases with which we have to deal with regard to postoponement of surgical intervention are those patients in whom obstruction is secondary to some inflammatory process such as a postoperative ruptured appendix, and that other often distressing group who have had more than one obstruction and, therefore, a number of laparotomies with the resultant widespread presence of adhesions. Conservatism in these two types will often be rewarded; also operation, which may become necessary, is often unsatisfactory as emphasized by Morton.[15]

Intestinal intubation as described by Miller and Abbott[16] not only has a definite place in the nonsurgical treatment of intestinal obstruction, but it is also particularly applicable to the two types of obstruction to which reference was just made, namely, that secondary to an inflammatory process and the recurrent type due to multiple abdominal adhesions. It is also true that there are a good many patients in whom gastric or even duodenal suction with the Levine tube will not afford very much relief from the distention. The principle of the Miller-Abbott tube is well known. There have been a number of modifications, but the most satisfactory is a double lumen tube with an inflatable balloon near the end. One lumen is used for the aspiration of intestinal gas and fluid while the other, which is connected with the balloon which surrounds the tube, can maintain any required degree of inflation. The tube as originally devised had what was termed a duodenal bucket on the end which had the dual purpose of assisting the tube through the pylorus and at the same time enabling its position to be located very easily under the fluoroscope. Other innovations have been used in its place, such as putting mercury in the balloon or attaching a small number of buckshot tied in a bag at the end of the tube, the purpose being to facilitate the passage of the tube through the pylorus. When the tube has once passed into the duodenum and the balloon has been partially inflated, there is no doubt that the tube will advance and decompress the bowel in the presence of either mechanical obstruction or adynamic ileus.

Encouraging results have been reported by Abbott and Johnston[17] and others with the use of intestinal intubation, but the method has definite limitations as well as many difficulties connected with its use. In the first place, it is a time-consuming measure even in the most experienced hands. It is frequently necessary to watch the course of the tube by fluoroscopy, which means constant handling of a patient whose general condition may be definitely precarious. The most serious drawback to this method in the hands of many physicians is the difficulty in getting, and indeed in many cases the failure to get, the end of the tube through the pylorus in any reasonable time. It is one of those procedures that should not be relied upon by the surgeon who has treated only occasionally a case of obstruction, but should be used in a properly selected group of cases by the surgeon who has had the opportunity and the patience to work with the method frequently and to devise his own maneuvers that will make the difference between success and failure. There are many procedures that have been described by various surgeons that are of great value in their

own hands because they understand their intricacies and know how to use them. In other hands, however, whether experienced or not, a particular procedure may not yield the same good results, a fact which is due to the personal equation that too often is not given the proper consideration. I feel that the use of the Miller-Abbott tube is in this category. If it is used in the proper group of cases by experienced hands it will prove a tremendous asset; if valuable time is wasted in attempting its use by those who are not familiar with it, the mortality rate will rise as a result. It should be added in justice to those who have developed this method that they have not advocated its use in the treatment of obstructions of the large bowel or if there is any indication of strangulation of the bowel. It is obvious that in the presence of strangulated hernia, temporization instead of operation may bring about disastrous results.

Up to the present point, the discussion has outlined the nonsurgical treatment of intestinal obstruction with due regard to the fact that operation for complete relief will be necessary in the great majority of cases. Naturally, if the patient responds to conservative measures and shows real improvement as contrasted with the false security that may be engendered in the surgeon following partial abdominal decompression and replacement of fluids and electrolytes, although the obstruction has not been relieved, operation may be safely deferred. When laparotomy is necessary the two measures already begun, which should be continued during the surgical operation, are the parenteral administration of fluids and syphon drainage of the stomach and upper intestinal tract. Drainage can be accomplished by letting the distal end of the duodenal tube, which has already been inserted, hang down over the edge of the operating table as low as it will and at the same time having it unclamped. This plan will allow the escape periodically during the operation of fluid or gas that may be forced upward by any necessary handling of the bowel. Often the nasal tube is clamped off during the period of the operation and this not only is not helpful to the surgeon but also may be definitely harmful to the patient.

There are certain measures that are necessary during the postoperative period to ensure the complete relief which both the patient and the surgeon desire. In the first place, gentle suction applied to the duodenal tube should be started again as soon as the patient has been returned to the bed. It is not possible to state any definite time during which suction should be continued, but in most cases it is well not to stop it until the patient has had at least one or two voluntary stools and the abdominal distention has definitely subsided. When this point has been reached it is wise to stop the suction and then clamp off the tube for periods of about two hours while at the same time the patient continues to take some fluid by mouth. If after this procedure has been repeated a number of times there is not much return of fluid from the tube when suction is reapplied, as a rule it is safe to remove the tube. It is usually at this time that the patient once again feels that he is really going to get well, and the surgeon feels considerable relief also. At times it is necessary to leave the duodenal tube in place for as long as a total of six to eight days; this can be done with surprisingly little discomfort to the patient when the tube is fixed with

adhesive tape at the point just below where it emerges from the nose in such a way that the tube cannot move in or out and so cause irritation.

The parenteral administration of adequate amounts of water, crystalloids, and protein in the proper proportion is, if possible, even more important after operation than it was before. In order to accomplish this it is necessary to correlate certain known daily requirements of the body with the total loss of fluids and waste products in any twenty-four hour period. In other words, it is necessary to keep an accurate account of the total fluid intake parenterally and orally, and also the total fluid output including drainage from the duodenal tube, urine excretion, and vomitus, if any. In this way it is possible to determine accurately whether the positive fluid balance which is so essential to the normal convalescence of the patient is maintained.

It has been shown experimentally and noted clinically by numerous observers that there is always a definite degree of adynamic ileus accompanying any mechanical obstruction. The degree of paralysis of the bowel is usually in direct proportion to the length of time that the obstruction has been present. When there is added the trauma incident to surgical operation for relief of the obstruction, even though this may be kept to a minimum, the problem with which we are faced after operation is to afford the patient relief from adynamic ileus. As has been mentioned, perhaps the most important step in accomplishing this result is to establish and maintain a positive fluid balance and also to add the proper amount of crystalloids and proteins parenterally until the patient is able to take the necessary requirements by mouth. As stated previously, if the average patient is given in a twenty-four hour period a minimum of 3,000 c.c. of water, 5 Gm. of electrolyte, 150 Gm. of glucose, and 50 Gm. of protein, he should remain in the proper balance. There should be, however, a minimum output of 1,200 c.c. of urine in each twenty-four hour period. If it is necessary to give additional fluid to maintain this output it is best to give it in the form of 5 per cent glucose in distilled water. This supplies extra nourishment as well as increases the urinary output. There is no reason why water should not be given to the patient by mouth by starting with small amounts very soon after operation, because with the suction maintained by the duodenal tube there is no danger of an accumulation in the stomach or upper intestinal tract. The patient obtains definite benefit from drinking water even if it is mostly of a psychic nature at first.

The role of drugs in the treatment of intestinal obstruction is not an important one, and there is considerable difference of opinion as to both their methods of action and their effectiveness. During the preoperative period drugs have very little place. Too often morphine is given when the possibility of intestinal obstruction is not suspected and the signs and symptoms are masked so that the true diagnosis is not made early and the institution of adequate treatment is delayed. Postoperatively, morphine has a definite place. As shown conclusively by Puestow,[18] morphine in moderate doses increases peristalsis in the small intestine but at the same time decreases it in the colon. However, he and others have shown that pitressin will stimulate peristalsis in the colon, and there is no doubt from clinical evidence that if a rectal tube is inserted just be-

fore an ampule of pitressin is given intramuscularly most patients with distention of the colon will respond very well. The only other drug that various investigators have reported as having any uniformly stimulating effect on the peristaltic action of the small bowel is prostigmine. A regimen which has proved satisfactory after operation in most cases of intestinal obstruction as far as the use of drugs is concerned, is to give morphine, usually ⅛ gr. but never more than ⅙ gr., as often as every four hours if necessary to give the patient reasonable comfort. At the same time, starting usually four hours after the patient has returned to the ward, 1 c.c. of pitressin may be given every four hours alternating with prostigmine, 1 c.c., every four hours. This means that for the first twenty-four hour period after operation the patient will receive pitressin and prostigmine alternately at two-hour intervals.

There are some surgeons who do not feel that enemas are of benefit in the treatment of intestinal obstruction. In 1936 Ochsner[19] stated categorically, "Enemas, flushes and cathartics have no place in postoperative treatment." For the rationale of this statement he pointed to the fact that in ileus the bowel is already distended and the musculature is functionally inactive, therefore, the patient will not be able to evacuate the fluid of the enema any more than he could his own gas and fluid. This will undoubtedly prove to be the case if large quantities of fluid are given or if an attempt is made to flush out the colon. If, however, a water and glycerin enema of not more than 250 c.c. is given not oftener than twice in each twenty-four hour period and is given just before the pitressin is due, excellent results will obtain in most cases. As Puestow[18] said, "Pituitrin or pitressin combined with enemas serves very well to relieve the distress by emptying the large bowel." After the patient has had a number of effectual enemas, their further employment depends entirely upon the clinical progress.

There are two other adjuvants in the postoperative treatment of intestinal obstruction that should be mentioned because there are times when they prove of definite benefit. The inhalation of 95 per cent oxygen as employed by Fine and others[20] has a sound theoretical basis, and when it is administered with a Boothby apparatus it can be done effectively and very economically. There are, however, many patients who do not respond, at least to this therapy alone, and it can be considered only as one more means which may be tried to help relieve distention. The other form of treatment that undoubtedly makes the patient feel more comfortable, although it is doubtful how much actual benefit he derives from it, is the application of heat to the abdomen. Hot stupes and dry heat have been advocated by physicians and surgeons for the relief of abdominal distention for many years, but it is questionable how much actual benefit has ever been derived therefrom.

SUMMARY AND CONCLUSIONS

It has been well stated by Veal[21] that "the mortality rate of acute intestinal obstruction is largely the mortality of delay and rises each hour that proper treatment is delayed." Because of the difficulty, first, in establishing a definite diagnosis of obstruction in many cases, and, second, of trying to determine how

far conservative treatment can be followed before operation is imperative, the task of carrying out "proper" treatment is not always an easy one. Certain essentials, however, can be enumerated as follows:

1. Restore lost fluids, crystalloids, and protein by parenteral administration without delay.

2. Be guided as to amounts that should be given by the clinical picture of the patient as well as the use of laboratory tests.

3. Establish suction drainage of the stomach and upper intestinal tract by means of a nasal tube immediately after the diagnosis of intestinal obstruction has been made.

4. Do not delay operation, particularly when cramplike pains persist after decompression of the stomach and upper intestinal tract.

5. Continue postoperatively the parenteral administration of proper amounts of fluid, crystalloids, and protein when necessary, until adequate amounts can be taken by mouth.

6. Continue suction drainage of the stomach until the bowels have moved and distention is relieved.

7. Use judiciously morphine, pitressin, and prostigmine together with small water and glycerine enemas; this is helpful in combating postoperative ileus.

8. It has been shown by the excellent reports of Veal[21] and of Moses[22] that the mortality rate of intestinal obstruction can be reduced to a low figure in obstructions of the small bowel by the proper combination of nonsurgical treatment with good surgical care. Comparable results can be obtained in obstructions of the large bowel as well.

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Book Reviews

Nursing in Commerce and Industry. By Bethel J. McGrath, R.N., New York. Pp. 356. New York, 1946, Commonwealth Fund. $3.

In preparing this volume Mrs. McGrath and the National Organization for Public Health Nursing have recognized the fact that although over 13,000 nurses were employed in this type of work during 1943 no book existed which attempted to delineate the scope of the industrial nursing program, the problems to be encountered, or the duties of the individual. Most of these nurses have had no special training or preparation for industrial assignment and most of them have been employed in programs that were lacking medical direction. It is little wonder under such circumstances that the industrial nursing programs have varied widely in their scope and quality and that the poorer programs were not in a position to benefit from the experience of the better ones.

This volume represents an attempt to bring together the experiences of many companies and individuals in the industrial nursing field. After several introductory chapters on the place of the nurse in the industrial organization, attention is given to various types of problems that will be encountered. Several of the chapters are written by collaborators.

It is inevitable that the reader will find much to criticize in a book of this character for it represents a pioneering excursion into a field where differences of opinion are great. Many will take exception to Mrs. McGrath's basic philosophy that industrial nursing is a field which a nurse may enter directly from a school of nursing rather than a specialty of public health nursing to be entered only after training and experience in the broader field. This philosophy has resulted in the inclusion of much material that would have been learned in the usual public health nursing course. Some will find her concept of the role of the nurse too broad while others will wonder if the program that is described may not be a deterrent rather than a stimulus to the development of adequate medical service in industry. Others will take exception to her concept of a nurse directly responsible to the top management and paid at the same rates as the executive heads of the other major departments of the industry.

Such questions and doubts are natural and desirable in reading a book which deals with a rapidly expanding and still unstable field characterized by highly divergent policies and opinions. Mrs. McGrath has attempted to portray these differences, although clearly expressing her own ideas. The reader will find the book stimulating and provocative and at the same time highly informative. In many places the information is extremely detailed, which will be of assistance to the nurse who enters this field without experience or training in public health. The author writes well and easily, but with frequent overindulgence in words. In many places the book could be condensed without loss while many other parts seem somewhat sketchy.

Criticisms of a volume of this character are obviously easy. They should not obscure the fact that the book fills a very real need, that it is packed with useful information to be found nowhere else and that it will stimulate much interest and discussion of an important field of both nursing and industry.

Acute Injuries of the Head, Their Diagnosis, Treatment, Complications and Sequels. By G. F. Rowbotham, B.Sc., Surgeon in Charge, Department of Neurological Surgery, Newcastle General Hospital, New Castle, England. Pp. 424, with 201 illustrations. Baltimore, 1945, Williams & Wilkins Company. $8.50.

This book was written primarily for those physicians who are responsible for the treatment of acute cerebral trauma and yet who have not received special training in neurology and neurosurgery. It is an effort to present a continuous picture of the problems arising

during the care of a patient with a head injury and an attempt to outline the treatment. Mr. Rowbotham is well qualified to edit this book because of his extensive experience both before and during the recent war. In this second edition, he has rewritten many chapters and has included experiences of British neurosurgeons in World War II. Throughout the book is stressed the fact that for good results and early readjustment following a head injury, a patient must have continuous and coordinated treatment beginning at the time of injury and continuing until he is resettled in employment.

The first section of the book concerns the mechanism of head injuries and includes a discussion of fracture patterns as well as the work of Dr. Holbourn of Oxford on the theory of injury to the brain by the forces of rotation. The section on pathology presents clinical rather than histologic studies of concussion, cerebral herniation, hematomas and hygromas, the development of the neurologic picture, and the cause of death in head injuries. In the section on diagnosis, signs diagnostic of the different types of head injury, special tests used, and graphs illustrating typical clinical stages of regression and of recovery are presented. Special signs such as delayed decerebrate rigidity, fixed dilated pupils, and prolonged unconsciousness are given as indications of poor prognosis. The section on closed injuries and on compound wounds is well written. The techniques advocated are standard; however, only briefly mentioned is the use of fibrin foam for hemostasis and of tantalum for cranioplasties. An adequate summary of the treatment of osteomyelitis of the skull is given. The highlight of the book is the section on the results of injury to special parts of the brain and skull. Injuries of the neural optic system are well discussed. The basic causes of the sequelae of head injuries, both organic and inorganic, are well evaluated. There is a chapter on rehabilitation in which the center at the Castle of Callaly is intimately described. The book ends with a chapter on the mechanism of birth injuries.

Important to students of head injuries is a well-indexed and extensive bibliography of the English, French, and German literature.

The book has the disadvantage of being written by one man with all the opinions and interpretations based on his experience; however, it is an invaluable contribution to a higher standard of treatment of head injuries.

Medicine in Industry. By Bernhard J. Stern, Ph.D., Lecturer in Sociology, Columbia University. Pp. 209. New York, 1946, Commonwealth Fund. $1.50.

There has long been need for a compact discussion of the community health problem occasioned by industrial employment and for an objective description of the various measures that have been tried to solve these problems. In this book Dr. Stern, who is sociologist maintaining teaching connection in both Columbia and Yale Universities, has provided such a volume. After a brief discussion of the awakening of our consciousness of the problem of industrial health, and somewhat longer consideration of the social and legislative background of modern industrial medicine, Dr. Stern presents a careful analysis of the present problems of industrial disability and the handicapped worker. He analyzes the preventive services now available, the successes and failures of health insurance plans, and the place of the industrial physician. He concludes that none of the methods now applied to American industry has been adequate to meet the needs for better prevention of hazards and comprehensive medical service within the financial capacity of the worker. Dr. Stern does not attempt to plead the case of any specific reform. The book represents merely a critical and highly objective appraisal of present problems. In preparing this volume for the series of monographs sponsored by the New York Academy of Medicine, Committee on Medicine and the Changing Order, Dr. Stern has produced the best available appraisal of the current status of the industrial hygiene movement. The book should be read carefully by all who are interested in this expanding field or who are concerned with the general problem of the changing patterns of medical practice.

Surgical Treatment of the Motor-Skeletal System. Edited by Frederick W. Bancroft, A.B., M.D., F.A.C.S., and Clay Ray Murray, M.D., F.A.C.S. Two volumes. Philadelphia, London, and Montreal, 1945, J. B. Lippincott Company. $20 a set.

The first volume deals with congenital and acquired deformities, paralytic disorders, affection of the back muscles, fasciae, tendons, bursae, and ganglia; new growths; diseases of bones and joints; and amputations. The second volume contains descriptions of fractures and dislocations; sprains, sprain-fractures, muscle and tendon injuries; birth injuries of the motor-skeletal system; and military surgery.

Outstanding men in each special field have contributed to these two volumes in an admirable fashion. The reviewer was a bit disappointed in a few of the subjects which were not completely described or supplied with an adequate bibliography.

These two volumes should serve most efficiently for the physician with a general practice, but the orthopedist or the surgeon who is interested in the treatment of bones and joints will not always find as complete a description of certain conditions as he would like. The book is recommended highly to the general man, but also is of sufficient interest to be on the bookshelf of the orthopedist.

The Extremities. By Daniel P. Quiring, Ph.D., Beatrice A. Boyle, Erna L. Borousch, M.A., and Bernardine Lufkin, A.B., Cleveland Clinic Foundation, Cleveland, Ohio. Pp. 117, with 106 illustrations. Philadelphia, 1945, Lea & Febiger. $2.75.

The authors have, in a series of clear, distinct diagrams, ably demonstrated the origin, insertion, action, and arterial and nerve supply of the muscles of the upper and lower extremities. Separate designation of the motor points of the muscle is also a noteworthy feature, for in most standard anatomic works, these points, which are of importance to the physician, are not given sufficient emphasis.

In the preface, the authors state clearly that the pitfalls of oversimplification of the actions of muscles are to be avoided by the reader, for it is only the primary function, which implies movements at the insertions, which is given in the text. One objection which might be raised in describing each muscle as a separate unit is that the importance of a group of muscles acting simultaneously to produce given movement is almost completely overlooked. However, the reader will find this monograph easy and worth-while reading.

Textbook of Neuro-Anatomy. By Albert Kuntz, M.D., Ph.D., Professor of Micro-Anatomy, St. Louis University School of Medicine, St. Louis, Mo. Pp. 478, with 328 illustrations. Philadelphia, 1945, Lea & Febiger.

The content and form of this book are very much the same as the third edition, although changes have been made—some new figures have been added, others have been replaced, redrawn, or otherwise changed.

On page 89, the statement is made that preserved pieces of nerves obtained from cadavers have been successfully used to bridge the gap between the proximal and distal segments of interrupted nerves. It does not seem proper that such controversial material should be stated as fact in a book of this type intended primarily for the early years of the medical school curriculum.

This is a good standard textbook of neuro-anatomy and should be valuable to medical students taking courses in this subject.

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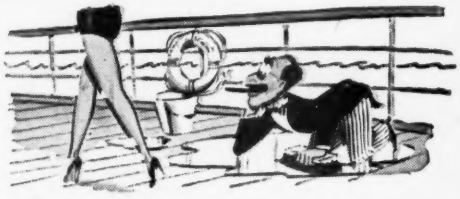

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